American Journal of Diseases of Children

VOLUME 61 APRIL 1941 NUMBER 4

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APHTHOUS PHARYNGITIS

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In the summer of 1938 my attention was called to the occurrence in a group of children of cases of a disease with a distinct clinical picture which I had not seen previously and which was not described in the standard pediatric textbooks. This disease was characterized by sudden onset with high fever, occasional episodes of moderate vomiting, acute inflammation of the throat, without much local soreness, disappearance of the fever in twenty-four hours and the appearance, frequently coincident with the drop in temperature, of a few discrete aphthous or canker-sore-like lesions on the upper portion of the tonsillar pillars.

In May 1939 Levine, Hoerr and Allanson [1] described an epidemic of what they termed "vesicular pharyngitis and stomatitis" which had occurred in three summer camps in New Hampshire during July and August of 1938. The illness which they described so closely resembles that which was seen in Rochester, N. Y., at the same time that one must assume that the same disease was present in both localities.

During the summer of 1939 I saw no similar cases, but during June, July and August of 1940 there was a second minor epidemic of the disease in Rochester. In 1938 8 cases were observed, and in 1939, 20. Other pediatricians likewise saw similar cases in the city at the same time.

The description of the disease by Levine, Hoerr and Allanson fits my cases so well that I quote from their paper.

> The disease was characterized by a sudden onset with headache, malaise and a variable degree of sore throat and fever, but the most significant finding (present in all of the cases) was the appearance in the throat of one or more yellowish white, slightly raised vesicles 1 or 2 mm. in diameter, usually surrounded by an intense red areola. These lesions were most frequently found on the faucial pillars (anterior more often than posterior), on tonsillar tissue when present or on the soft palate. . . . Only one or two lesions might appear in the entire

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1. Levine, H. D.; Hoerr, S. O., and Allanson, J. C.: Vesicular Pharyngitis and Stomatitis: An Unusual Epidemic of Possible Herpetic Origin, J. A. M. A. **112**:2020-2022 (May 20) 1939.

course of the illness, or the entire visible pharynx might be studded with them. The lesions often occurred in small clusters, which later coalesced. In most instances the individual or coalescent vesicles ulcerated, leaving a shallow punched-out, grayish yellow crater measuring from 2 to 4 mm. in diameter; some lesions never ulcerated. The lesions disappeared in from five to ten days, usually outlasting the fever.

In a few . . . cases . . . the mucosa adjacent to the vesicles became deeply injected and even hemorrhagic, with moderate edema, simulating the so-called streptococcic sore throat.

. . . The soreness of the throat was usually not severe . . . several of the patients with marked ulceration had no soreness whatever.

TABLE 1.—*Age Distribution of Patients with Aphthous Pharyngitis*

Age, Months	Number of Patients
Under 12	0
13 to 24	5
25 to 36	3
37 to 48	6
49 to 60	7
61 to 72	1
Over 72	6
Total	28

TABLE 2.—*Maximum Temperature in Twenty-Six Cases of Aphthous Pharyngitis*

Temperature (F.)	Number of Cases
Under 100	2
100 to 100.9	1
101 to 101.9	1
102 to 102.9	3
103 to 103.9	14
104 to 104.9	4
105 to 105.9	1
Total	26

Although the group of patients of Levine and his associates was larger than mine (106 and 28, respectively), their patients were youngsters of camp age and attendants (from 7 to 67 years old), older, in general, than the children I observed (table 1). This disparity in age may account for some of the minor differences in the clinical pictures presented by the two groups of patients.

The usual comment of the mothers of my patients was that the children were feverish but did not seem sick except for listlessness and anorexia. Most of the mothers were puzzled by the sudden onset of the disease, which was usually first noticed in the late afternoon or early evening. Most of the younger children had a temperature of between 103 and 104 F. (table 2). There was also a surprising lack of symptoms. Vomiting, as already mentioned, occasionally occurred, and in the case of a 11 year old boy it was, except for some malaise and slight headache, the only symptom.

In a number of the children who were seen early in the course of the disease, numerous petechiae dotted the soft palate and anterior tonsillar pillars; the aphthous lesions appeared later. In general, the ulcerations or aphthous lesions were more marked after the fever subsided. Although in 6 of 23 cases the fever and malaise lasted several days, in the majority (17) the temperature was normal within twenty-four hours of onset and the child played as if nothing had happened, although the aphthous lesions were still present in the throat.

The lack of pain and discomfort in the throat was in marked contrast to the misery associated with cases of the so-called aphthous or herpetic stomatitis in children. The duration of the illness and the limitation of the lesions to the back part of the throat are also different from the clinical characteristics of the latter disease. In only 1 case did I see a lesion anterior to the anterior tonsillar pillars, and that was a single one on the buccogingival margin.

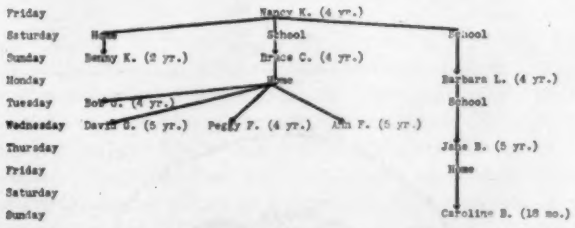

Fig. 1.—Course of an outbreak of aphthous pharyngitis in a nursery school.

Levine and his associates stated that 50 per cent of the campers under and 25 per cent of those over 18 years of age who were exposed contracted the disease. Sixteen siblings of patients in my series were exposed to the disease. Of these, 6 contracted the illness, 5 escaped it and for 5 the result of the contact was not known. To my knowledge, the parents of none of the affected children contracted the illness.

For the camp series the incubation period could not be determined, although 2 subjects came down with the disease five and seven days, respectively, after arriving in camp. From this it was concluded that the incubation period could not be much longer than a week. I was able to determine the incubation period in a number of my cases. A small outbreak occurred in a local nursery school attended by my oldest child (5 years of age). Although most of the patients were not seen by me personally, the fathers of several of the children were physicians, and the time intervals between cases could be determined. In all cases the symptoms of the disease were characteristic: sudden onset of high fever, mild malaise, sore throat and, in 1 child, vomiting. The duration of the fever was approximately twenty-four hours in all cases. The course of the outbreak in the school is depicted in figure 1.

There were four other groups of cases for which it seemed possible to ascertain the incubation period. In all, there were 10 cases in which the time relation to a previous case could be determined with reasonable accuracy. Of these, the incubation period (to the nearest twenty-four hours) was one day in 1, two days in 2 and three days in 7. In the case in which one day elapsed between the appearance of the disease in the first child and its appearance in the other, it is possible that the patients had had a common contact several days previously.

The laboratory data were not characteristic. In the series of cases of Levine and his co-workers twelve blood counts were made during

TABLE 3.—*White Cell Counts for Five Patients with Aphthous Pharyngitis*

Patient	Total White Cell Count	Percentage of Polymorphonuclears	Highest Temperature (F.)
Betsy A.	11,200	52	104
Robert D.	12,700	66	102
Mary W.	7,200	62	104
David G.	12,200	..	103
Gregory G.	10,750	..	103

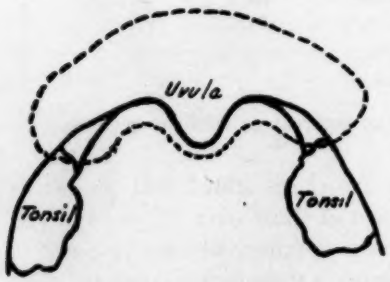

Fig. 2.—Area of the throat (indicated by dotted line) which was involved in patients with aphthous pharyngitis.

the first three days of the disease. The leukocyte counts ranged between 5,500 and 11,000 per cubic millimeter. In my series of cases five white cell counts were made on the first day of the disease (table 3), and the results agree with theirs.

In the New Hampshire series bacteriologic examination by means of direct smears, cultures or both was carried out in 51 cases. Pneumococci seemed to be the predominant organisms, but it was not believed that they were the etiologic agent. In 2 cases blood cultures were sterile. An attempt to demonstrate herpes virus by inoculating the corneas of rabbits with material from 2 patients failed.

Cultures were made at the height of the fever in 5 of my cases. No hemolytic streptococci or pneumococci were found. However, in

4 of the 5 cultures hemolytic Staphylococcus aureus was present, but I do not believe that this is significant. A single attempt to demonstrate a virus in material obtained from a patient within a few hours of onset was unsuccessful.[2]

SUMMARY

Characteristics of 28 cases of an unusual type of pharyngitis are described. The cases occurred in the summers of 1938 and 1940. Sudden high fever, mild subjective symptoms and inflammation of the soft palate and the pillars of the tonsils, with the appearance of aphthous lesions in the same area, are the clinical characteristics of the disorder. Except for the lesions in the throat, the duration of symptoms is about twenty-four hours. The incubation period is approximately three days. The cause of the disease is unknown.

REPORT OF CASES

CASE 1.—The mother of Judith M., aged 3 years, first noticed that the child had high fever in the afternoon after she had awakened from her nap. I saw the patient at my office within a few hours of onset. The results of the physical examination were entirely normal except for acute inflammation of the throat. In the midline of the soft palate, which was red and slightly edematous, there were scattered petechiae. Three or four aphthous lesions surrounded by red areolas were present on the anterior pillars of the tonsils. Her temperature was 104 F., but she did not appear sick. The following day her temperature was normal and she seemed well. The lesions in the throat were still present.

CASE 2.—Between sixty and sixty-five hours after the onset of Judith's illness, Denny, her 16 month old sister, was found to have a temperature of 102 F. At that time her throat was inflamed and edematous, and petechiae were present in the same area of the throat as had been involved in her sister's case. The following day aphthous lesions surrounded by areas of acute inflammation appeared over the pillars of the tonsils and on the soft palate and her temperature rose to 103 F. The throat seemed to be sore. The following day her temperature was normal and she appeared well, although the lesions in the throat did not clear up completely for several days.

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2. A suspension of material for inoculation was obtained by having the patient gargle with 10 cc. of meat extract broth. This material was expectorated and was immediately put in the refrigerator. Twelve hours later 0.2 cc. of the broth was applied to the scarified cornea of a rabbit and the remainder was filtered through a Berkefeld V candle. The filtrate of the material was used for the inoculation of animals as follows: One rabbit received 0.25 cc. intracerebrally and 1 cc. intraperitoneally; 3 guinea pigs were given injections of 0.1 cc. intracerebrally and 0.5 cc. intraperitoneally and 6 mice were given 0.05 cc. intracerebrally and 0.5 cc. intraperitoneally. The animals did not react to either the unfiltered or the filtered suspension.

Dr. Jerome Syverton, of the department of bacteriology of the University of Rochester, who carried out this work, does not believe that this single failure rules out the possibility that a virus is the etiologic agent of the disease.

CASE 3.—Suddenly and without other symptoms except irritability and listlessness, fever temperature of 103 F. developed in Ruth H., aged 2 years. Some anorexia was present. She was seen within a few hours of onset. In an area on the margin of the soft palate and over the anterior tonsillar pillars which were acutely inflamed, a few aphthous lesions were present. Her temperature was 104 F. The remainder of the physical examination gave normal results.

CASE 4.—When Mrs. H. was told what was wrong with Ruth, she mentioned that the child's sister Margaret, aged 7 years, had felt "mopey" and had complained of sore throat the previous day but that she had felt well that morning and had gone to school. Examination of Margaret showed acute inflammation of the throat and several punched-out shallow ulcers in the area of the soft palate and the anterior pillars of the tonsils. Apparently she had had some fever the day before, but none was present at this time, and the lesions of the throat gave rise to no subjective symptoms at the time she was examined.

Both children had played four days previously with a child reported to have been ill shortly thereafter.

Although Margaret apparently lost her subjective symptoms in one day, Ruth did not recover for three days.

CASE 5.—Jimmy McD., aged 12 years, came to my office for a routine inoculation against hay fever. His mother stated that the day before he had vomited four or five times, had complained of headache and some malaise and had said that his throat felt "scratchy." Slight fever had been present. Examination showed that on the lower border of the soft palate near the uvula there was a single aphthous lesion, 4 to 5 mm. long and 1 to 2 mm. wide. It was punched out and surrounded by a red areola. At the time of the examination the patient had no complaints.

CASE 6.—Fever (temperature of 103 F.) developed in Barbara B., aged 9 years, and she complained of headache and generalized aching. She said that her throat was dry but not sore. Results of a physical examination were normal except for redness of the soft palate and the pillars of the tonsils and the presence of three or four aphthous lesions on the anterior tonsillar pillars. The following day her temperature was normal, she felt well and she went to school in the afternoon.

CASE 7.—Fever (temperature 102 F.) developed suddenly in Robert D., aged 17 months. He did not seem sick, and his appetite was only slightly disturbed, although he was more irritable than usual. Examination showed a moderately injected area in the region of the soft palate and the tonsillar pillars. That night his temperature rose sightly. The next morning he seemed perfectly well and his temperature was normal. Examination of the throat showed several aphthous lesions on the left tonsillar pillar.

MEASURE OF METABOLIC SPEED IN CHILDREN

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The basal metabolic rate, that is, the measure of the level of energy expenditure necessary to maintain basal metabolic processes, is the resultant of multitudinous and unceasing biochemical reactions; on these biochemical reactions depend the integrity of the body and the normal function of its cells. This so-called metabolic speed is innately controlled by the vegetative nervous system. Any constitutional aberration in basal metabolic behavior obviously provokes a disturbance in fundamental body phenomena. The clinical, the biologic and the social significance of such a disturbance will be considered in subsequent studies.

As a prelude to our major study of constitutional dyscrasias in children, it was necessary to determine the most efficient laboratory procedure by which to measure, record and compare rates of basal metabolism.

STANDARD METHODS OF DETERMINING METABOLIC SPEED

Three well known methods serve in the estimation of metabolic speed: namely, the assessment of skeletal development, the determination of the basal metabolic rate and the measurement of the total cholesterol of the serum. These measures will be commented on in sequence.

Assessment of Carpal Development.—Skeletal development and, inferentially, general bodily maturation may be measured roentgenologically. For such an examination, the carpal centers are the most accessible; assessment of their development by persons of unequal experience has given consistent results. "Assessment of the hand shows the smallest standard deviation and is, therefore, the skeletal area which gives the most generally satisfactory results." [1] The clinician in applying the measure of skeletal development to determine the bodily maturation has preferred to assess carpal development. For these reasons data have been limited to the results of examinations of the bones of the wrist. For all patients with delay in skeletal development a low metabolic rate was found. As a consequence, clinicians and roentgenologists have syllogistically assumed that delay in maturation, a retarded bone age, is

1. Todd, T. W.: Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937, p. 19.

a measure of the hypothyroid state and of the metabolic rate.[2] Shelton [2a] stated: "Bone age is a reliable index of metabolic speed in childhood." Shepardson [3] stated: "Normal bony development predicates normal body metabolism. Uniformly there is to be found a definite retardation of ossification which, generally speaking, parallels the degree of thyroid deficiency [page 687]." Skeletal development and metabolic speed, therefore, are assumed to be parallel and commensurate. We question the logic and validity of such a conclusion.

Determinations of Basal Metabolic Rate.—The clinical measure of the metabolic rate is imperfect. Since a true basal state can never be accurately attained, the consumption of oxygen can be determined only under approximately standard conditions of rest and fasting. From such data, the basal metabolic rate is best calculated in terms of calories per square meter of body surface.[4]

Various adventitious factors and the momentary mental and physical state of the subject may disturb the conditions under which such a test is given and may render the result inaccurate. Thus standard conditions are difficult to ascertain. The value for the basal metabolic rate used in any study should be that determined by the first test conducted;[5] the element of training is thereby excluded. It must be understood that there is no single true basal metabolic rate for each subject.[5]

The range of normal values is most frequently reported as from + 10 to — 10 per cent. All deviations from the theoretic normal value, zero, are expressed as percentage variations. Basal metabolic rates can be determined for children over 2 years of age.[6]

Measurement of the Total Cholesterol.—"In most, if not all persons in health, the amount of cholesterol in the serum appears to be maintained at a constitutional level which is characteristic for each individual and from which large deviations do not ordinarily occur."[7] The con-

2. (*a*) Shelton, E. K.: Endocrinology **17**:667-676 (Nov.-Dec.) 1933. (*b*) Goldzieher, M.: The Endocrine Glands, New York, D. Appleton-Century Company, Inc., 1939, p. 139. (*c*) Todd,[1] p. 22. (*d*) Rotch, T. M.: Tr. A. Am. Physicians **24**:603-624, 1909. (*e*) Wilkins, L.: Thyroid Medication During Childhood, J. A. M. A. **114**:2382-2386 (June 15) 1940.

3. Shepardson, H. C.: Radiology **26**:685-699 (June) 1936.

4. Murlin, J. R., in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1939, vol. 1, p. 134.

5. Boothby, W.; Berkson, J., and Dunn, H.: Am. J. Physiol. **116**:468-484 (July) 1936.

6. Talbot, F. B.: Internal Secretory System and Metabolism in Infancy and Childhood, in Haynes, R. S.: Clinical Pediatrics, New York, D. Appleton and Company, 1928, vol. 13.

7. Sperry, W., Jr.: J. Biol. Chem. **117**:391-395 (Jan.) 1937.

stancy of such a level is not grossly altered by the intake of food or by seasonal influences.[8]

Two pertinent questions arise: First, what numerical value represents the average level of total cholesterol in the serum of children, and, second, in what manner and to what extent does the level of total cholesterol change with alteration in constitutional adequacy? In answer to the first question, the usually accepted average level of total cholesterol of the serum in children, between the neonatal period and puberty, ranges between 100 and 164 mg. per hundred cubic centimeters of blood.[9]

In answer to the second question, many investigators have demonstrated a qualitative, or inverse, relation between the level of total cholesterol and the basal metabolic rate.[10] When, however, the basal metabolic rate is altered by nonconstitutional factors, such as drugs, the level of total cholesterol remains unchanged.[11]

Whether a quantitative relation, that is, a significant correlation, exists between the level of total cholesterol and the basal metabolic rate is, however, in dispute.[12]

MATERIAL AND METHODS

In a private pediatric practice, determination of basal metabolic rate, measurement of total cholesterol and assessment of carpal development were routine procedures. For this study, data on 216 subjects, selected at random, for whom two or more of these measures had been made, were used. Correlations of these accumulated data were made by the Pearson product-moment method. Our intent was to establish the relative validity of each procedure as a measure of metabolic speed.

Controlled conditions prevailed throughout this investigation. In each case, all measures were initial and concurrent determinations. All tests for determin-

8. Turner, K., and Sterner, A., Jr.: J. Clin. Investigation **18**:45-49 (Jan.) 1939.

9. Molitch, M., and Poliakoff, S.: Arch. Pediat. **53**:613-616, 1936. Rothbart, H.: Basal Metabolism in Children of Normal and Subnormal Intelligence, with Blood Cholesterol and Creatinine Values, Am. J. Dis. Child. **49**:672-688 (March) 1935. Ward, K. M.: Arch. Dis. Childhood **6**:329-342 (Dec.) 1931. Gørtz, S.: Acta pædiat. **19**:553-556, 1937. Cohen, G., cited by Lyttle, J. D.: Laboratory Pediatrics, in Haynes, R. S.: Clinical Pediatrics, New York, D. Appleton and Company, 1930, vol. 20. Faber, H., and Roberts, D., Jr.: J. Pediat. **3**:78-83 (July) 1933.

10. Hurxthal, L.: Blood Cholesterol and Hypometabolism, Arch. Int. Med. **53**:824-831 (June) 1934. Boyd, E. M., and Connell, W. F.: Quart. J. Med. **6**: 467-471 (Oct.) 1937.

11. Hurxthal, L., and Hunt, H.: Ann. Int. Med. **9**:717-727 (Dec.) 1935.

12. Gilligan, D. R.; Volk, M. C.; Davis, D., and Blumgart, H. L.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: Relationship Between Serum Cholesterol Values, Basal Metabolic Rate and Clinical Aspects of Hypothyroidism, Arch. Int. Med. **54**: 746-757 (Nov.) 1934. McGee, L.: Ann. Int. Med. **9**:728-737 (Dec.) 1935.

ing basal metabolic rate were conducted under identical conditions, which included overnight fasting, omission of all matinal food and fluids and a rest of one hour preceding the test. The same room, bed, box mattress and covering were used for all tests, and the temperature and humidity were constant. The child usually remained alone until the test was run. The McKesson metabolor was selected for these determinations; its constantly moving roll of chart paper made it possible to teach the child to breathe satisfactorily and also to select the most representative portion of the curve. In computing the basal metabolic rate the body surface standards of Du Bois were used. The total cholesterol was measured during the same fasting state by the modified Bloor method.[13]

The 216 patients, clinically constitutionally inadequate, included 125 boys and 91 girls. Their age range was representative of that encountered in the average pediatric practice (table 1). Sex differences were not significant. The differences between the mean ages of the boys and the girls and between the mean age for either sex and that for the total group were likewise not significant.[14]

TABLE 1.—*Age Distribution of Two Hundred and Sixteen Patients with Constitutional Inadequacies* *

	Number of Patients	Age Range, Years †	Mean Age	Standard Deviation
Boys	125	1 to 14	6 yr. 5 mo.	3 yr. 8 mo.
Girls	91	1 to 14	6 yr.	3 yr. 3 mo.
Total	216	1 to 14	6 yr. 3 mo.	3 yr. 6 mo.

* Constitutional inadequacies are defined as specific disorders or inabilities which are inherent in the makeup of the person, are not situationally or accidentally determined, and prevent him from coping successfully with environmental situations.

† The ratio of boys to girls is approximately the same in all the quartiles of the age range. This assures no overweighting of either sex at any particular part of the range. In Q_1, or the youngest 25 per cent of the patients, ages ranged from 1 year 6 months to 4 years 5 months; in Q_2, they ranged from 4 years 6 months to 6 years 4 months; in Q_3, from 6 years 5 months to 9 years 11 months, and in Q_4, or the oldest 25 per cent of the patients, from 10 to 14 years.

RESULTS

The results of our determinations of basal metabolic rate, level of total cholesterol and carpal development (bone age) were analyzed according to (1) the age range of the patients for whom each of the three measures was determined and (2) the interrelations of the three measures.

Age Range for the Three Measures.—The age range, 1 to 14 years, was the same for all groups, with two exceptions: The age range for the 9 girls with retarded bone age was 5 to 10 years, and that for the 7 girls with advanced bone age was 1 to 7 years (table 2).

13. Determinations of the basal metabolic rate and the total cholesterol were made by Miriam Spicer, of the Setzler Laboratories; roentgenograms of the carpal bones were assessed by Dr. C. C. Hopkirk.

14. Significance of the difference of the means is obtained by the formula:

$$\text{C. R.} = \sqrt{\sigma M_1^2 - \sigma M_2^2} \qquad \left(\sigma M = \frac{\text{S. D.}}{\sqrt{N}}\right)$$

To be significantly different, the difference between the means must be at least 3 × C.R. (critical ratio).

The mean age of the group of patients for whom the basal metabolic rate was determined was significantly higher than that of the other groups. Basal metabolic tests are less frequently done on patients in the younger age groups.

Relation of Age, Sex and the Three Measures.—Between age and sex and the three measures of metabolic speed—the basal metabolic rate, the level of total cholesterol and the bone age—no significant relation was demonstrated (table 3).[15]

TABLE 2.—*Age Distribution of Patients for Whom the Three Measures Were Determined*

Factor Measured	Sex	Number	Age Range of Patients, Yr.	Mean Age	Standard Deviation
Basal metabolic rate....	Boys	89	1 to 14	7 yr. 10 mo.	3 yr. 2 mo.
	Girls	66	1 to 14	7 yr. 1 mo.	3 yr. 10 mo.
	Both	155	1 to 14	7 yr. 6 mo.	3 yr.
Level of total cholesterol	Boys	112	1 to 14	6 yr. 6 mo.	3 yr. 9 mo.
	Girls	70	1 to 14	5 yr. 6 mo.	3 yr. 3 mo.
	Both	182	1 to 14	6 yr.	3 yr. 7 mo.
Bone age					
(1) Patients with retarded bone age	Boys	47	1 to 14	6 yr. 11 mo.	2 yr. 10 mo.
	Girls	9	5 to 10	7 yr.	
	Both	56	1 to 14	6 yr. 11 mo.	2 yr. 9 mo.
(2) Patients with normal bone age	Boys	53	1 to 14	5 yr.	3 yr. 10 mo.
	Girls	49	1 to 14	5 yr. 6 mo.	2 yr. 8 mo.
	Both	102	1 to 14	5 yr. 2 mo.	3 yr. 4 mo.
(3) Patients with advanced bone age	Both	7	1 to 7	3 yr. 11 mo.	
(4) Patients of groups 1, 2 and 3...		165	1 to 14	5 yr. 7 mo.	3 yr. 4 mo.

TABLE 3.—*Correlations of Age and the Three Measures*

Factor Measured	Age
Basal metabolic rate	—0.06 - 0.014
Level of total cholesterol	—0.10 - 0.03
Bone age	—0.21 - 0.04

Relation of Basal Metabolic Rate and Level of Total Cholesterol.—For the 127 cases in which the basal metabolic rate and the level of total cholesterol were determined, the coefficient of correlation between the two measures was -0.65 ± 0.03. This coefficient shows a direct and highly significant relation between the high level of total cholesterol and the low basal metabolic rate. The validity of this relation was further portrayed by comparing the mean basal metabolic rates for the quartiles of the levels of total cholesterol; there is a significant difference between the rates for the first and the fourth quartile (tables 5 and 6). The mean levels of total cholesterol for the first three quartiles of the range of basal metabolic rates do not depart strikingly from the mean level of total

15. The Pearson product-moment coefficient of correlation was used throughout the study.

cholesterol for the entire range (202.5 mg. per hundred cubic centimeters of blood). No general rise in the values for the mean level of total cholesterol accompanies a decrease in values for the basal metabolic rate, as seen in table 5 (except for the sudden change in the fourth quartile);

TABLE 4.—*Range of Basal Metabolic Rates, Levels of Total Cholesterol and Retardation in Bone Age*

Factor	Sex	Number	Range *	Mean	Standard Deviation
Basal metabolic rate, per cent.....	Boys	89	—1 to —38	—18.7	8.1
	Girls	66	—6 to —38	—19.2	7.0
	Both	155	—1 to —38	—18.9	7.7
Level of total cholesterol of blood, mg. per 100 cc.	Boys	112	167 to 289	201.3	18.9
	Girls	70	173 to 277	204.0	14.3
	Both	182	167 to 289	202.5	15.9
Bone age, of chronologic age retarded, percentage.....	Both †	56	2 to 62	20.4	12.5

* There is no significant difference between the mean metabolic rates and mean levels of total cholesterol for the boys and the girls or between the means for either sex and those for the total group.

† As there were only 9 girls presenting evidence of delay in carpal development, the values for this measure were not shown by sex.

TABLE 5.—*Mean Levels of Total Cholesterol for Quartiles of Range of Basal Metabolic Rates*

	Number	Range of Basal Metabolic Rates, per Cent	Mean Level of Total Cholesterol, Mg. per 100 Cc. of Blood	Standard Deviation
Q_1.....	32	— 1 to —10	202.4	20.5
Q_2.....	35	—11 to —18	205	18.2
Q_3.....	31	—19 to —24	200.5	10.6
Q_4.....	29	—25 to —38	213.5	22.1

TABLE 6.—*Mean Basal Metabolic Rate for Quartiles of Range of Levels of Total Cholesterol*

	Number	Range of Levels of Total Cholesterol, Mg. per 100 Cc.	Mean Basal Metabolic Rate, per Cent	Standard Deviation
Q_1.....	30	167 to 185	—14.2	7.4
Q_2.....	30	186 to 197	—18.9	5.6
Q_3.....	32	198 to 212	—21.5	7.2
Q_4.....	35	213 to 289	—21.3	7.5

nevertheless, the relation between these two factors is more apparent in table 6. There is a significant difference between the mean basal metabolic rates for the first and fourth quartiles of the range of levels of total cholesterol. The data in tables 5 and 6 indicate that the low basal metabolic rate is more closely related to the high level of total cholesterol than the high level of cholesterol is to the low basal metabolic rate.

Relation of Basal Metabolic Rate and Bone Age.—Measures of basal metabolic rate and bone age, judged by carpal development, were

obtained in 110 cases. The retardation in bone age, present in 44 cases, ranged from 2 to 62 per cent of the chronologic age. Normal bone age was found in 59 cases. For the correlation of the basal metabolic rate and the percentage of retardation in bone age the coefficient is -0.23 ± 0.016 (table 7). This coefficient shows the lack of any relation between the low basal metabolic rate and the percentage of retardation in bone age. The two factors are not measures of each other.

The mean basal metabolic rate was statistically the same for all patients, whether the bone age was retarded, advanced or normal. Carpal development (bone age) cannot be considered a measure of basal metabolic rate.

TABLE 7.—*Mean Basal Metabolic Rates for Bone Age Series*

Bone Age	Number	Range of Basal Metabolic Rates, per Cent	Mean Basal Metabolic Rate, per Cent	Standard Deviation
Normal	59	— 2 to —36	—18.4	6.0
Delayed	44	— 1 to —38	—17.8	7.2
Advanced	7	—13 to —22	—18.2	

TABLE 8.—*Mean Level of Total Cholesterol for Bone Age Series*

Bone Age	Number	Range of Levels of Total Cholesterol, Mg. per 100 Cc. of Blood	Mean Level of Total Cholesterol, Mg. per 100 Cc. of Blood	Standard Deviation
Normal	83	170 to 271	200.7	17.4
Delayed	46	172 to 264	199.9	14.6
Advanced	7	195 to 242	216	

Relation of the Level of Total Cholesterol and Bone Age.—These measures were obtained for 129 patients. Of these, 46 patients were delayed in their carpal development by from 2 to 62 per cent of their chronologic age; 7 showed an advance in bone age of from 8 to 400 per cent of their chronologic age, while 88 had a normal bone age.

The coefficient of correlation between the high level of total cholesterol and the percentage of retardation in bone age is -0.016 ± 0.013. The mean level of total cholesterol was statistically the same for all patients, whether the bone age was retarded, advanced or normal. No relation is thereby shown between delay in carpal development and the high level of total cholesterol (table 8).

Relation of Basal Metabolic Rate, Level of Total Cholesterol and Retardation in Bone Age.—In 44 cases the basal metabolic rate and the level of total cholesterol were determined and the delay in carpal development was assessed.

The coefficients of correlation between the percentage of delay in carpal development and the basal metabolic rate and the level of total

cholesterol, respectively, are -0.23 and ± 0.016. No relation was shown between the level of total cholesterol, the basal metabolic rate and the delay in carpal development. The number of cases is hardly sufficient. The mean percentage of delay in carpal development is not related to either the lowness of the basal metabolic rate or the highness of the level of total cholesterol (tables 9 and 10).

TABLE 9.—*Mean Percentages of Retardation in Bone Age for Quartiles of the Range of Basal Metabolic Rates*

	Range of Basal Metabolic Rates, per Cent	Percentage of Retardation * in Bone Age
Q_1	−1 to −10	20
Q_2	−11 to −18	21.7
Q_3	−19 to −24	17.3
Q_4	−25 to −38	18.3

* Retardation is expressed in percentage of chronologic age.

TABLE 10.—*Mean Percentages of Retardation in Bone Age for Quartiles of the Range of Levels of Total Cholesterol*

	Range of Levels of Total Cholesterol, Mg. per 100 Cc. of Blood	Percentage of Retardation * in Bone Age
Q_1	167 to 185	21
Q_2	186 to 197	20.7
Q_3	198 to 212	22.5
Q_4	213 to 289	18.1

* Retardation is expressed in percentage of chronologic age.

COMMENT

A simple, valid laboratory test was necessary to estimate the level of maintenance metabolic activity. Current medical opinion differs as to the reliability of pertinent measures. Many physicians, for example, accept determinations of carpal development and basal metabolic rate as corollary measures of metabolic speed. The level total cholesterol is not used independently as a routine measure of metabolic activity but serves, rather, as a confirmatory test, supplementary to the determination of the basal metabolic rate.

Discrepancies were apparent in the results obtained by all three measures and in their clinical interpretation. To check their validity, we measured concomitantly the basal metabolic rate, the bone age and the total cholesterol. The data obtained were examined statistically; results to be meaningful and definitive must be authenticated mathematically.

Basal Metabolic Rate.—The determination of the basal metabolic rate, a sensitive mechanical measure of oxygen utilization, is affected by the adventitious influences of the moment. Inconsistencies, therefore,

will arise when standard conditions of mental and physical rest and abstinence from drugs do not prevail. A careful technic and controlled conditions are essential in giving the test; these requirements were fulfilled in the conduct of our study. The clinical determination of the basal metabolic rate measures the maintenance metabolic activity under standard conditions. The results obtained ultimately indicate the relative tempo not only of biologic oxidations but of nutritional supply for maintenance and growth. Such phenomena condition the adequacy of all biologic functions. These biologic functions are the bases for the various somatic and psychologic adjustments of the child to his total environment. For these reasons, the reliable measure of "metabolic speed" is of inestimable value in the attempted correction of constitutional dyscrasias.

The range of normal basal metabolic rates is generally accepted as from + 10 to — 10 per cent. We believe that many of the rates considered normal are incorrectly assessed. To substantiate this belief, supplementary measures of the total cholesterol and the degree of carpal development were made for 32 patients whose basal metabolic rates fell within the range of 0 to — 10 per cent. The results contradicted their supposed normalcy. In this group the average level of total cholesterol was 202.4 mg. per hundred cubic centimeters of blood (table 5). Eleven patients had basal metabolic rates which fell within the range of 0 to — 10 per cent, an average delay in carpal development of 20 per cent and a mean level of total cholesterol of 202.4 mg. per hundred cubic centimeters of blood (tables 6 and 9). When the value for a patient's basal metabolic rate lies within normal limits, the normalcy of the rate must then be authenticated by other measures.

It is the general impression that basal metabolic rates cannot be determined successfully for children under 8 or 9 years of age. Our experience is to the contrary. Basal metabolic rates were successfully determined for children from 1½ to 14 years of age. Our series of patients was broken down into four age groups. The patients in the first, or youngest, group ranged in age from 1 year 6 months to 4 years 5 months, while those in the fourth, or oldest, group were from 10 to 14 years old. The validity of the basal metabolic rates determined for our youngest group of patients is affirmed by the following: The average basal metabolic rate and the average level of total cholesterol were the same in both the youngest and the oldest age group.[16]

Subjects.—The age range of the children examined was representative of that encountered in the average pediatric practice. Neither age nor sex significantly influenced the data obtained. According to our data, when the basal metabolic rate, the degree of carpal development

16. Two measures of low maintenance metabolic activity were obtained in 75 cases; reliability equaled + 0.85.

and the level of total cholesterol are obtained for children with hypometabolism, neither age nor sex needs to be considered (tables 2, 3 and 4).

Carpal Development.—Since delayed skeletal development frequently becomes normal on thyroid medication, a relation has been assumed between delay in maturation and slow metabolic speed. Clinicians and roentgenologists consequently have accepted the assessment of carpal development in children as a measure of metabolic speed.

For our patients with delay in carpal development the average basal metabolic rate was — 17.8 per cent and the average level of total cholesterol was 199.9 mg. per hundred cubic centimeters of blood (tables 7 and 8). The generally accepted corollary, that all patients with slow metabolic speed have a delay in bone development, is not valid. Retarded bone age does not indicate a low basal metabolic rate. This fact is shown statistically by the coefficient of correlation, -0.23 ± 0.016, between the basal metabolic rate and the percentage of delay in carpal development. The coefficient of correlation, 0.016 ± 0.13, shows no relation between the level of total cholesterol and the percentage of delay in carpal development.

Carpal development in our constitutionally inadequate children was normal, delayed or advanced. In each of the three groups the average basal metabolic rate and the average level of total cholesterol were statistically identical. The extent or percentage of delay in carpal development, therefore, is not commensurate with the lowness of the basal metabolic rate or with the highness of the level of total cholesterol (tables 9 and 10). When, therefore, carpal development is the sole measure used to determine metabolic speed, a low metabolic rate and a high level of total cholesterol will not be recognized in 64 per cent of the patients. Only 36 per cent of those patients with a significantly low basal metabolic rate and a significantly high level of total cholesterol showed a retardation in bone age.

All our patients with delayed carpal development had slow metabolic speed; yet delay in carpal development was not present in all our patients with slow metabolic speed (table 7). The two conditions may or may not, therefore, occur together. In our opinion, they are concomitant variables, resultants of a common causal factor or group of factors.[17] These are deeply rooted in the metabolic substrate of the organism. As such, they may not be measures of each other.

Carpal development is solely a measure of skeletal maturation, and maturation follows the pattern of mammalian development. It can be normal only under conditions of good health. General constitutional fitness, and not the influence of a single controlling factor, determines the normalcy of the maturational pattern.[18]

17. Talbot, F. B., and Talbot, N. B.: J. Pediat. **16**:646-652 (May) 1940.
18. Shepardson,[3] p. 12.

An advance in carpal development exceeding one year, stated Todd,[2c] predicates not only constitutional fitness but freedom from any constitutional disturbances during the past. Our data positively contradict this statement. In every patient with advanced carpal development, hypometabolism was present (tables 7 and 8). Statistical accuracy, however, will necessitate a much larger series of cases.

It is of interest that of our 56 patients with delayed carpal development, only 9 were girls, while 47 were boys (table 2).

Level of Total Cholesterol.—The level of total cholesterol is constant; it is relatively unaffected by food intake or by seasonal or climatic variances; the procedure for determining it is simple and economical.

The range of levels of total cholesterol is 167 to 289 mg. per hundred cubic centimeters for our series of constitutionally incompetent children. The data coincide with the normal values cited in the literature. The high level of total cholesterol is a corollary of the low basal metabolic rate.

Our data reveal that the level of total cholesterol is the most valid of all measures of slow metabolic speed. By using it, the measure of metabolic speed becomes a feasible routine procedure for all children, newborn to adolescent. It will be found of tremendous value for prophylaxis.

In clinical studies, the interrelation of the level of total cholesterol and the basal metabolic rate has never been clearly assessed. Normal values, usually accepted, for total cholesterol range from 100 to 164 mg. per hundred cubic centimeters. The values in this grouping are an admixture of results of determinations of both the total cholesterol of the blood and the total cholesterol of the serum. We found no significant difference between the results obtained by the macromethod and by the micromethod.

Interrelation of the Level of Total Cholesterol and the Basal Metabolic Rate.—By statistical methods, corresponding groups of basal metabolic rates and levels of total cholesterol were compared (tables 5 and 6). The ranges of basal metabolic rates and the levels of total cholesterol were divided into quartiles. The data were analyzed quantitatively. The first quartile, with a range for the levels of total cholesterol of 167 to 185 mg. per hundred cubic centimeters, had an average basal metabolic rate of — 14.25 per cent, while the fourth quartile, with the highest level of total cholesterol, 213 to 289 mg. per hundred cubic centimeters, had the lowest average basal metabolic rate, — 21.31 per cent. Between the high level of total cholesterol and the low basal metabolic rate a significant correlation was obtained, -0.65 ± 0.03. When, therefore, the level of total cholesterol is known, the approximate basal metabolic rate can be inferred (table 6).

The lack of relation between the mean level of total cholesterol and the quartiles of the range of basal metabolic rates appears to be a paradox but can be explained. For all but the lowest basal metabolic rates, extraneous influences, both mental and physical, render the test only grossly significant. The measure of the total cholesterol is subject to no such error. When we attempted to establish an interrelation of the two factors by measuring from the least accurate, the basal metabolic rate, to the more exact, the level of total cholesterol, no significant relation was obtained by critical ratio. When, therefore, the basal metabolic rate is known, one cannot infer the level of total cholesterol. The only exception occurs in the lowest range of basal metabolic rates; these extremely low values are not altered by adventitious factors (table 5).

Interrelation of Bone Age and Low Metabolic Speed.—If bone age is a reliable measure of low metabolic speed, a positive correlation, or interrelation, must exist between bone age and metabolic speed. A low basal metabolic rate with a high level of total cholesterol must be present in all patients with retardation in bone age, and, likewise, retardation in bone age must be found in all patients with a low basal metabolic rate and a high level of total cholesterol. But the correlation coefficient of -0.23 ± 0.016 shows no relations (tables 9 and 10). The measure of bone age determines an approximate maturational level; as such, an indigenous low level of a maintenance metabolic activity is present. The measures of the total cholesterol and the basal metabolic rate serve to determine metabolic speed. The bone age, on the one hand, and the measures of the total cholesterol and the basal metabolic rate, on the other, fundamentally, therefore, subserve different functions, even though they may be remotely related.

CONCLUSION

The assessment of delay in carpal development is not a measure of "slow metabolic speed."

Determination of the level of total cholesterol is a simple and valid measure of a low level of maintenance basal metabolic rate activity in children.

Determinations can be satisfactorily accomplished for children beyond the age of 2 years.

When the basal metabolic rate is within the so-called normal limits of + 10 and — 10 per cent, its normalcy must be authenticated by measures of both the total cholesterol and the skeletal development.

Determinations of basal metabolic rate are less reliable than are determinations of total cholesterol as measures of "slow metabolic speed."

Dr. Charles Gilmore Kerley and Dr. E. Kost Shelton read the manuscript of this paper.

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PAROXYSMAL TACHYCARDIA AND ITS TREATMENT IN YOUNG INFANTS

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The following 9 case reports are presented to call attention to the clinical features of paroxysmal tachycardia as it occurs in infants less than 1 year of age. This study has been limited to this age group because in older children paroxysmal tachycardia is more readily recognized, has been described more often and seems to be similar to the form of the disorder that occurs in adults in that it sometimes appears in short attacks of no consequence and occasionally continues or recurs in persistent fashion and is more or less resistant to the various forms of treatment used. On the other hand, in young infants, especially during the early weeks of life, there appears to be a somewhat different and distinctive clinical entity, readily diagnosed if kept in mind, which responds satisfactorily to proper treatment. Failure to detect paroxysmal tachycardia in the young infant may lead to such faulty diagnoses as congenital idiopathic hypertrophy of the heart or pneumonia and may be of serious consequence to the patient.

In considering tachycardia in infancy, it is important to remember certain differences between the infant and the adult. In the first place, the pulse rate during the early weeks of life is rapid and unstable, varying normally between 110 and 140. Excitement or illness may readily elevate the rate to 180 or more. One who is unaccustomed to examining infants might be led to make a diagnosis of paroxysmal tachycardia on the basis of a pulse rate of 180 which is due, for example, to pneumonia with simple sinoauricular tachycardia. On the other hand, it is easy to make the mistake of paying too little attention to a rapid rate in a sick infant. It takes considerable skill and experience to count pulse rates of 200 or more, and yet it is important to do so in order to avoid overlooking the possibility that abnormal tachycardia is the true cause of the illness.

In the second place, the conduction of impulses within the heart of the infant appears to differ in certain respects from that in the heart of the adult. The commonly accepted definition of paroxysmal tachycardia in the adult is a condition marked by a pulse rate of usually 150

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to 200 which arises from an ectopic focus in the auricles, in the auriculoventricular node or, rarely, in the ventricles. It is, in a sense, a series of premature systoles, with a ventricular response to each auricular contraction. Auricular flutter is the term applied to the condition in which the auricles are beating at an excessively rapid and regular rate, 200 or more, the ventricular musculature being spared extreme activity by a greater or a lesser degree of block, so that the ventricles do not respond to each of the auricular stimuli. For example, the auricles may have a rate of 240 and the ventricles a rate of 120 beats per minute, which gives rise to a 2:1 ratio. Various such ratios are encountered. In infants abnormal tachycardia is associated with higher ventricular rates, usually 250 to 300 (tables 1 and 2). For patients with these rapid rates, the electrocardiagram is often difficult to interpret, as is well demonstrated by the difference of opinion found in the literature in regard to whether certain records should be considered as evidence of paroxysmal tachycardia of auricular or of auriculoventricular nodal origin or whether they are illustrative of auricular flutter with a 1:1 ratio. If distinct P waves can be identified, an accurate interpretation is usually possible. P waves preceding essentially normal-looking ventricular complexes locate the ectopic focus in the auricles. Impulses arising in the auriculoventricular node have retrograde stimulation of the auricles, producing P waves which are usually inverted and are superimposed on or follow the ventricular complexes (figs. 3 and 12). In differentiating between paroxysmal tachycardia and auricular flutter with a 1:1 ratio, rhythmic and regular undulations of the base line have been described as diagnostic of flutter. However, such undulations could be due to P and T waves superimposed or in rapid succession without any separating isoelectric period (figs. 4 and 10). If one is fortunate enough to have a record made as the tachycardia breaks into a normal rate, there may be found a clue to the situation. When the ectopic focus cannot be definitely determined, it seems wise to be content with a diagnosis of supraventricular tachycardia, in contrast to that of distinctive ventricular tachycardia, which is associated with a much graver prognosis.

In reviewing the literature, if one accepts only those cases in which there was graphic demonstration of the tachycardia and excludes any in which the rapid pulse rate might have been due to an accompanying illness (von Bernuth), one finds comparatively few cases. Extensive search has revealed only 19 well established cases of paroxysmal tachycardia or auricular flutter in infants less than 1 year of age. Data in these cases are listed in table 1. It is of considerable interest that the clinical features of these cases are altogether similar to those of the group of cases discussed later.

TABLE 1.—*Previously Reported Cases of Paroxysmal Tachycardia or Auricular Flutter in Infants Less Than One Year Old in Which the Rates Were Established by Polygram or by Electrocardiogram*

Author	Year	Age at Onset	Electrocardiogram Rate	Digitalis Preparations Given	Comment
Werley	1925	4 days	307*	No	Death at 6 days of age; patent foramen ovale
Blue	1926	2 mo.	270	No	Recovery
Colgate and McCulloch	1926	24 days	291	No	Recovery
Poynton and Wyllie	1926	4 mo.	250	Yes	Recovery
Russell and Ellison	1927	4 mo.	270	No	Recovery (no response to quinidine)
Doxiades	1930	7 days	240	No	Recovery
Carr and McClure	1931	Before birth	Flutter † 375:170	No	Recovery
Hecht	1932	8 days	Flutter † 300:170	No	.....
Duken	1933	2 wk.	300	No	Recovery
Sherman and Schless	1934	1 mo.	Flutter † 464:232	Yes	Recovery
Farr and Wegman	1935	3 wk.	300	Yes	Recovery
Wegman and Egbert	1935	10 mo.	240	Yes	Death; rhabdomyosarcoma of conducting system
Soeters	1936	4 mo.	300	Ouabain and quinidine	Recovery
Campbell	1937	1 mo.	300	Yes	Recovery
Lyon	1937	1 mo.	310	No	Death after 3 weeks, of streptococcic meningitis
Taran and Jennings	1937	7 days	250–300	Yes	Recovery
Powers and LeCompte	1938	8 mo.	200	No	Death; diagnosis of "idiopathic hypertrophy"
Puglisi	1939	10 days	345	No	Death; no response to quinine
Puschel	1939	27 days	275	Yes	Recovery

* This rate was determined by polygram, all others by electrocardiogram.
† Auricular flutter, with ratio of auricular rate : ventricular rate.

TABLE 2.—*Data on Nine Cases of Paroxysmal Tachycardia in Infants Less Than One Year Old*

Case	Age at Onset	Early Symptoms	Determinations During the Attack					Estimated Duration of Attack, Days
			Pulse Rate	Temperature, F.	Leukocytes	Pulmonary Congestion	Enlargement of Liver	
1. D. R. (1930)	1 mo.	Limpness and pallor; labored breathing	270	102	12,200	+	+	8
2. C. M. (1934)	4 mo.	Vomiting; pallor; rapid heart rate	300	104	27,900	+	+	1½
3. E. K. (1937)	3 wk.	Labored breathing; vomiting; grayish cyanosis	274	101	22,500	+	+	5
4. J. C. (1939)	2 wk.	Vomiting; pallor; rapid respirations	300	102	.....	+	+	4
5. R. B. (1939)	1 mo.	Labored breathing; vomiting	260	102	11,700	+	+	3
6. W. M. (1939)	3 wk.	Vomiting; pallor; rapid heart rate	290	99	22,300	?	+	2
7. M. B. (1939)	7 mo.	Labored breathing; rapid heart rate	305	103	39,400	Pneumonia	+	?
8. M. C. (1940)	10 days	Rapid heart rate	270	99	14,200	—	+	2+
9. C. C. (1940)	13 days	Cyanosis; rapid respiration	220	101	12,500	+	+	1

In contrast to the sparsity of cases previously reported is the frequency with which they have been observed here in a relatively short space of time. Of the 9 new cases reviewed in this paper 6 were observed during the course of one year. This indicates that such cases may occur more often than the number heretofore recognized would indicate. All of these cases were in infants less than 1 year of age (see the case summaries). That they cannot be considered as instances of simple tachycardia due to an accompanying illness is indicated by the cardiac rates and the clinical features.

In all the cases the patients had ventricular rates varying from 220 to 305, demonstrated electrocardiographically (figs. 1-4, 6 and 9-12). In all cases the tachycardia was of supraventricular origin. Cases 3 and 9 were interpreted as examples of tachycardia of auriculoventricular nodal origin. In most of the others upright P waves preceding the ventricular complexes were identified in at least one of the three standard leads, which located the ectopic focus in the auricles. In none was there clear proof of auricular flutter.

The age at onset in 7 of the 9 cases was within the first month of life. The youngest patient was a baby (case 8) born normally in a maternity hospital, with no unusual symptoms until tachycardia was noted, at the age of 10 days, by virtue of a routine examination before discharge. How long it had been present is impossible to say. Cases have been reported in the literature in which an abnormal rate has been found before birth (Carr and McClure, and Tollass).

The tachycardia may be associated with some other illness, or it may start with no evident cause. In case 4 there was evidence of intracranial damage, probably on the basis of birth trauma. In case 7 there was an area of pneumonic consolidation shown roentgenographically. In the other 7 cases there was no apparent precipitating event.

If the tachycardia continues, congestive failure develops, and it is usually the symptoms of failure, although they are not always recognized as such, that draw the attention of the parent or the physician to the fact that the baby is ill. In the cases presented here there was a rather consistent clinical syndrome (table 2). Vomiting occurred almost invariably, and in case 5 it was so severe as to suggest a diagnosis of pyloric stenosis. Characteristically, the baby becomes limp and has a dusky, grayish color, with obvious prostration. Careful observation will show the heart is beating at a rate which may be too fast to count. The radial pulse usually cannot be felt. The heart enlarges rapidly and may become greatly dilated. If the condition progresses congestive failure develops. Severe dyspnea ensues, with a remarkably high respiratory rate, sometimes as high as 150 to 160 per minute. The liver becomes engorged, its edge descending to the iliac crest. The spleen may become palpable. Considerable distention of

the abdomen may result. There may be some dependent edema. The temperature, if not already elevated, rises to 102 F. or more. Considerable leukocytosis develops. Roentgenographic examination of the chest shows, in addition to the enlargement of the cardiac shadow, evidence of pulmonary congestion (fig. 7).

The attack may stop spontaneously, or it may progress to a fatal termination if proper treatment is not instituted. In case 2 of the series reported here, in which the tachycardia had started only six hours before the patient was admitted to the hospital, treatment was withheld and the pulse rate dropped to normal on the second day. In the other 8 cases the attack stopped after the administration of digitalis. That death may result is demonstrated by certain cases in the literature. In Werley's case the patient died on the sixth day of life, the tachycardia having been noted on the fourth day. Postmortem examination showed a patent foramen ovale, an observation of doubtful significance at this age. In Lyon's case the patient died of streptococcic meningitis and erysipelas after prolonged paroxysmal tachycardia. In the case reported by Powers and LeCompte, death was attributed to congenital idiopathic hypertrophy of the heart. The electrocardiogram, which is reproduced in their report, showed a rate of 200 and was interpreted as indicating paroxysmal tachycardia probably of A-V nodal origin. The question can be raised as to the possibility that death in this case resulted from congestive heart failure due, in turn, to the paroxysmal tachycardia. In Puglisi's case, death rather obviously was due to the tachycardia and heart failure.

When the tachycardia subsides, the temperature and the respiratory rate fall to a normal level (fig. 8). The heart, which has been acutely dilated, may show a prompt decrease in size (fig. 7). The engorgement of the liver and the spleen disappears, with a return of the edge of the liver to the level of the costal margin (fig. 5). There is often marked diuresis, with consequent loss of weight. The color and the activity of the infant usually show dramatic improvement, and a baby critically sick one day may appear well the next.

The frequency with which patients with tachycardia have shown a significant rise of temperature with the development of failure and have become afebrile as the attack ceased reopens the question of the association of fever and congestive failure, which has been much discussed. Cohn and Steele found that in 153 of 172 cases of heart failure fever was present, a symptom which they attributed to the failure. More recently Kinsey and White have reviewed 200 cases of congestive failure, in all but 4 of which there was fever. Careful study disclosed complications in these cases which they considered adequate to account for the fever. The most common complications were pulmonary infarction, pulmonary infection, rheumatic infection and

coronary thrombosis. It is rather hard to picture any of these factors, except pulmonary infection (bronchopneumonia), playing a role in the cases presented here. In only 1 of the present series of cases was there roentgenographic evidence of pneumonia. In the others the pulmonary congestion, together with the fever, promptly disappeared as the tachycardia subsided. These cases, then, support the view that there is an association between congestion itself and fever.

The diagnosis of paroxysmal tachycardia in infancy should present no great difficulty if the condition is kept in mind. Failure, however, to detect abnormally fast heart rates may, as already mentioned, lead to confusion which can be of serious consequence to the patient. For example, dyspnea, cyanosis, fever, leukocytosis and cloudiness of the pulmonary fields, which have almost invariably appeared as a result of congestive failure, readily suggest a diagnosis of pneumonia. Or, again, the sudden onset of circulatory failure, with enlargement of the heart, leading to death, with nothing found at autopsy except cardiac enlargement and passive congestion, is consistent with the condition originally described by Howland as congenital idiopathic hypertrophy of the heart. In a recent report (Bonaba and Saldún de Rodríguez), a syndrome "of unknown etiology" occurring in nurslings is described as being characterized by prostration, depression, vomiting, spasmodic cough, dyspnea, cyanosis, increase in the cardiac volume from acute dilatation of the heart, hepatomegaly, edema, anasarca and ascites. These symptoms so closely resemble those in the cases of the present series that one is eager to know the pulse rate, of which no mention is made. Also, a case of acute cardiac decompensation was reported in 1 of a series of infants born of mothers with diabetes (Miller and Ross). In this case it was noted that the pulse rate was fast, although it was thought not to be excessive. It seems likely that counting of the pulse rates of infants is a much neglected procedure, and it is worth repeating that carrying out this procedure is important in order to avoid overlooking the presence of paroxysmal tachycardia, which responds so satisfactorily to proper therapy.

In the treatment of tachycardia in infants digitalis has, in my experience, been the drug of choice. The simpler procedures which may stop an attack in an adult, such as pressure on the carotid sinuses or the eyeballs or induction of vomiting, are rarely effective for infants. In many of the cases reported in the literature, the patients received a wide variety of drugs other than digitalis, such as quinine, quinidine, physostigmine, pilocarpine and morphine. None of these was of much value. Mecholyl chloride (acetylbetamethylcholine hydrochloride), which has been found effective for older children and for adults, was used in case 6 of this series. Sudden and alarming circulatory failure, with collapse, followed its administration. Electrocardio-

grams, which were taken continuously, showed ventricular pulsations occurring irregularly about every two seconds. Atropine was given intravenously at once, and its administration was followed by a return to the original rate of 290 (see the case report). A similar alarming reaction to mecholyl (acetylbetamethylcholine) in the treatment of paroxysmal tachycardia in an older child has recently been reported by Walsh and Sprague. In view of such reactions as these and of the uniformly satisfactory experience with digitalis, it seems wise to consider the use of mecholyl only if other treatment fails.

Digitalis or one of the digitalis preparations, when given in adequate amounts (dosage is discussed later), has invariably been effective in stopping the tachycardia. In all of my cases except case 2, in which the patient recovered spontaneously, digitalis was used, generally in the form of digifoline, given subcutaneously (table 3). Also in the cases

TABLE 3.—*Summary of Digitalis Therapy of Paroxysmal Tachycardia in Nine Infants*

Case	Patient's Weight, Pounds	Dose of Digitalis Required to Stop Attack
1. D. R.	8	Digitalis, 0.12 Gm. in 2 days
2. C. M.	8½	Attack stopped on second hospital day
3. E. K.	9	Digifoline, 0.3 Gm. in 2 days
4. J. C.	8¼	Digifoline, 0.1 Gm. in 1 dose
5. R. B.	8½	Digifoline, 0.3 Gm. in 1 day
6. W. M.	7	Digifoline, 0.15 Gm. in 1 day
7. M. B.	18	Digifoline, 0.3 Gm. in 1 day
8. M. C.	7½	Digifoline, 0.1 Gm. in 1 dose
9. B. C.	13¾	Digifoline, 0.1 Gm. in 1 day

from the literature in which digitalis was given in large enough doses, there was a satisfactory response,[1] except for the case with fatal termination reported by Wegman and Egbert, in which the tachycardia stopped but the patient died and was shown to have had a rhabdomyosarcoma of the conduction system.

There is uncertainty in regard to what constitutes the proper dose of digitalis for infants. It is often stated in pediatric literature, especially in the German, that infants require more digitalis per pound (0.45 Kg.) of body weight than adults. Clinical experience has to a certain extent confirmed such statements. To the infants in this series of cases the usual plan has been to give an intial dose of 0.05 to 0.1 Gm. of digifoline intramuscularly. The drug has been administered

1. In the case reported by Taran and Jennings, the electrocardiographic tracings made after the administration of digitalis were reported by the authors to show ventricular fibrillation, and hence they concluded that digitalis therapy in cases of paroxysmal tachycardia in young infants may be accompanied by considerable danger. However, close inspection of the published record leaves room for doubt, for there were wide excursions of the base line which look as if they might have been due to somatic action rather than to ventricular fibrillation.

intramuscularly because of the difficulty of medication by mouth in these small infants, who are usually vomiting. Repeated doses of 0.05 to 0.1 Gm. have been given as indicated. In case 3, 0.3 Gm. of digifoline was given to a 9 pound (4,082 Gm.) baby during the course of two days. This amount was required to obtain the desired results. However, experimental evidence fails to support clinical experience in regard to the need of proportionately larger doses of digitalis for infants. Haag and Corbell have recently reported on a study of the effect of the age of cats on the susceptibility to digitalis, using a variety of standardized preparations. They found no significant difference between the dose per kilogram for young kittens and that for adult cats. Therefore, until more is known about the dosage of digitalis for infants, caution should be used in giving infants and young children much larger amounts per pound of body weight than have been accepted for adult use.

After digitalization in most of the 9 cases reported on here, the cardiac rate and rhythm returned promptly to normal. In none was auricular flutter shown to be present by an auricular rate faster than the ventricular. In case 8 there was a period of temporary auricular fibrillation (fig. 11), occurring directly after the tachycardia had stopped. Sometimes after the prolonged attack of tachycardia, there seems to have been a period during which there may have been instability of the pacemaker, as shown by variations in the P waves (cases 3 and 9). In 4 of the cases in this series (cases 3, 4, 6 and 8) there were short attacks of tachycardia after the rate had dropped to normal. The patient in case 3 had several short recurrent attacks for about two weeks. The patient in case 4 had one other attack a week after the first one. The patient in case 6 had none that the parents were aware of and seemed well on all return visits to the clinic, but in the electrocardiographic tracings there was evidence of recurrent attacks for about three months. The patient in case 8 had a few short attacks for three days while being given maintenance doses of digitalis and none subsequently. The remaining 5 patients (cases 1, 2, 5, 7 and 9) had no recurrent attacks. To those who showed a tendency to recurrence of the rapid rate, a maintenance dose of digitalis, usually about 0.05 Gm., was given daily until the episodes of tachycardia ceased. In none of the cases studied so far has there been any persistent tendency for the tachycardia to recur, and in all except the last one the patients have been observed for at least six months since the attack for which they were hospitalized.

As a result of this experience and a careful study of the literature, it may be said that episodes of paroxysmal tachycardia in young infants may be severe or even fatal if untreated but that the disorder responds satisfactorily to digitalis and, so far as continued observation to date has shown, the disease appears not to have the tendency to recur

which is so often manifest in older children and in adults. However, six months is admittedly too short a time to permit any definite statement concerning the latter point. Further observation will be needed to determine whether as they grow older these infants do remain free of paroxysmal tachycardia.

SUMMARY

Nine cases of paroxysmal tachycardia occurring in young infants are reviewed. The fact that 6 of these were observed during one year stands in contrast to the sparsity of well established cases in the literature and indicates that such cases may occur more often in the early months of life than has heretofore been recognized.

In these 9 cases and in 19 collected from the literature, in all of which the infants were less than 1 year old, there is a distinctive clinical course which in certain respects differs from that in cases of paroxysmal tachycardia in older children or in adults. The heart rate is usually 250 to 300, and if the tachycardia continues for several days, as it is likely to do, it brings on circulatory failure, which is associated with vomiting, dyspnea, fever, leukocytosis, cardiac enlargement, pulmonary congestion and engorgement of the liver. Failure to bear in mind the possibility that paroxysmal tachycardia is present in a young infant may lead to such misdiagnoses as pneumonia or congenital idiopathic hypertrophy of the heart. Paroxysmal tachycardia in young infants may be severe and may have a fatal termination if untreated, but so far as present experience indicates, the disease responds satisfactorily to adequate doses of digitalis.

REPORT OF CASES

CASE 1.—D. R., a male infant, was born normally at full term and at birth weighed 6 pounds 7 ounces (2,920 Gm.). During the first two weeks of life it was noted that he tired easily when nursing. During the next two weeks he seemed better, but he continued to tire at the breast and to fall asleep. At the age of 4 weeks he had a severe crying spell, after which he became limp and pale and broke into a profuse perspiration. During the next five days he continued to have similar episodes, which were severe but were not associated with convulsive spasms or twitchings, and he breathed rapidly.

At the age of 5 weeks he was admitted to the Infants' Hospital. On physical examination he appeared acutely ill, with marked respiratory distress. The respirations were rapid, with periods during which he held his breath and became cyanotic. The lungs were clear. The heart was considerably enlarged. The tip of the spleen was palpable. An electrocardiogram taken the following day showed paroxysmal tachycardia, with a rate of 270 (fig. 1). At the same time a teleroentgenogram showed marked enlargement of the cardiac shadow. The transverse diameter of the heart was 7.1 cm., and the internal diameter of the chest, 11.5 cm. There was a considerable amount of diffuse fine mottling in the lungs, which was considered to be on the basis of passive congestion. Repeated urinalyses gave normal results. The hemoglobin content was 70 per cent; the erythrocyte count was 3,350,000 per cubic millimeter, and the white

cell count was 12,000 per cubic millimeter, with 60 per cent neutrophilic leukocytes. His weight was 8 pounds (3,629 Gm.).

During the second and third days in the hospital he was given 0.12 Gm. of digitalis by mouth, in divided doses. On the third day in the hospital (two days after treatment with digitalis was started) his pulse rate for the first time dropped to a normal level. His temperature fluctuated between 99 and 102 F. during the first three days, while the tachycardia persisted. On the third day, when the tachycardia subsided, his temperature became normal and remained so. There was marked clinical improvement. The administration of digitalis in small doses was continued for nine days. There was no recurrence of tachycardia during the three weeks the baby remained in the hospital.

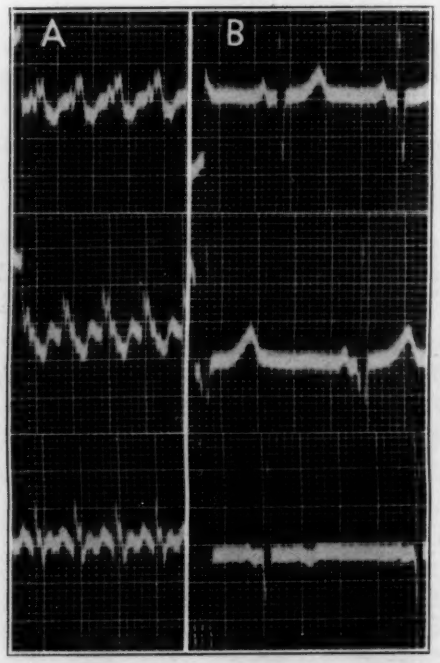

Fig. 1 (case 1).—*A*, May 28: paroxysmal tachycardia supraventricular, or possibly ventricular. Rate 270. *B*, June 2: normal rate, 80. (This and all the subsequent electrocardiograms show the three standard leads.)

CASE 2.—C. M., a female infant, was born normally at full term. The weight at birth was 6 pounds 2 ounces (2,778 Gm.). She had a cough from birth which precipitated vomiting twice a day. Because of this she received a variety of formulas and medications. The cough became worse during her second month of life, and she was therefore admitted to the hospital, where she remained for two weeks.

At this time there was evidence of pharyngitis, bilateral otitis media and bronchopneumonia. The heart was considered normal, with a normal pulse rate, although there is no record of her pulse rate at that time. A roentgenogram of the chest showed a considerable amount of mottled pulmonary infiltration on both

sides, most marked medially. From this a diagnosis of bronchopneumonia was made. Her temperature remained normal. Her cough persisted, but she was allowed to return home after two weeks of hospitalization.

At the age of 4 months she was readmitted because of an extremely rapid heart rate, which had been noted by her family physician. She had progressed satisfactorily in the interval up to this time, with her cough gradually becoming less. Six hours before admission she refused feedings, vomited and became pale.

On physical examination at entry, she appeared pale and listless, with rapid, shallow respirations. There was evidence of otitis media on the left. The heart appeared slightly enlarged on percussion, with a rate estimated at 240. No murmurs were heard. The liver was enlarged. An electrocardiogram showed a rate of 300 (fig. 2), and a diagnosis of paroxysmal tachycardia was made. The teleroentgenogram showed slight enlargement of the heart. The transverse diameter of the heart was 6.1 cm., and the internal diameter of the chest, 11.4 cm. The temperature was 104 F. Her weight was 8½ pounds (3,856 Gm.).

On the second day the rate dropped to normal and the temperature fell to normal and remained so. Her color improved, as did her general condition. After the rate reached a normal level a systolic murmur was heard over the apex. She had received no digitalis.

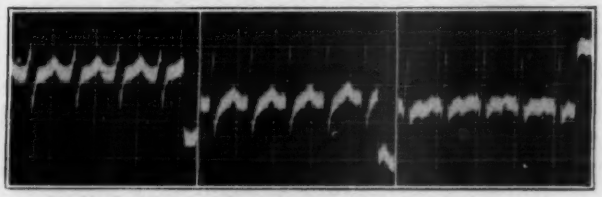

Fig. 2 (case 2).—Paroxysmal tachycardia, auricular; right axis deviation. Rate 300.

It was estimated that the duration of her attack was from six hours before to thirty-two hours after hospitalization. She had no return of tachycardia. She was seen again at the age of 6 months because of continued clinical signs of pulmonary infection. At this time the soft, blowing systolic murmur was heard over the apex that had been heard previously; so in addition to the diagnosis of pulmonary infection a questionable diagnosis of congenital malformation of the heart was made.

CASE 3.—E. K., a female infant, was born of normal, healthy parents on Aug. 25, 1937. The weight at birth was 7 pounds 6 ounces (3,345 Gm.). The baby was free from postnatal disturbances and was considered normal by the obstetrician. She had a routine pediatric examination at the age of 2 weeks. At this time the heart was considered normal, with a normal rate, and no murmurs were heard.

On September 13, at the age of 3 weeks, it was noted that the baby breathed heavily. The following day she vomited twice and became fussy. On September 15 she appeared to be in poor condition, with a grayish color. The temperature was normal. The respirations were rapid, the rate being about 160 per minute. No rales were heard. The pulse rate was thought to be about 200 per minute. There was considerable cyanosis. The abdomen was distended.

The baby was admitted to the hospital. A roentgenogram of the chest made on admission showed considerable cloudiness on both sides, more marked in the

hilar regions but extending well out into the parenchyma. There was enlargement of the heart, the transverse diameter of the heart being 5.9 cm. and the internal diameter of the chest 10.6 cm. The white cell count was 22,500 per cubic millimeter. The red cell count, the hemoglobin content and the differential count were essentially normal. Her weight was 9 pounds (4,082 Gm.).

The same day the baby became worse. Rales were heard posteriorly over both lungs. There was an increase in cyanosis, and the baby was placed in an oxygen tent. The pulse continued rapid, with the rate recorded as 200 to 280. The respirations continued rapid, the rate being about 120. The edge of the liver was 2 to 3 cm. below the costal margin, and the tip of the spleen was palpable.

Fig. 3 (case 3).—*A*, September 16: paroxysmal tachycardia, auriculoventricular nodal or possibly auricular, with long PR interval. Rate 274. *B*, September 18: Irregular rhythm, with rate of approximately 110. The P waves now show marked variation, indicating a shifting pacemaker. *C*, September 29: normal rhythm. Rate 160, which is within normal limits for this age. Note the change in time marking, which gives a false impression of the rate in comparison with that in *A* and *B*.

On the following day, September 16, the baby appeared critically sick, with a pale, grayish color and marked cyanosis when crying. The pulse and respiratory rates continued as on the previous day. The temperature, which had been normal, rose to 101 F. There was increasing enlargement of the liver. An electrocardiogram taken on the same day (fig. 3*A*) showed a regular rhythm, with the rapid rate of 274. Digitalis therapy was started, with an initial dose of 0.1 Gm. of digifoline given intramuscularly. Subsequent doses of 0.05 Gm. were given at intervals, so that she received 0.3 Gm. during two days.

On September 17 the baby became progressively worse, with continuation of the rapid pulse and the rapid, labored respirations. There was further increase in the size of the liver, the edge of which was now felt at the level of the umbilicus.

On September 18, two days after digitalis was started, it was noted that the baby voided frequently, her abdomen became less distended and her color and general condition improved. The heart rate fell to a level of 120 to 140. Respirations became more normal. There was striking improvement during the day, and she was therefore removed from the oxygen tent. The improvement continued during the next few days. The temperature, which had fluctuated between 99 and 101 F., dropped to normal and remained normal throughout the subsequent course. A roentgenogram, taken on September 20, showed marked improvement in the lungs. The congestion previously noted had disappeared, so that the pulmonary fields were clear. The heart showed no significant change in size. Maintenance doses of digifoline (0.05 Gm.) were given at intervals of two or three days.

On September 24 there was a temporary elevation of the pulse rate to over 200. Episodes of tachycardia recurred for brief periods in the next four days, during which daily doses of digifoline (0.05 Gm.) were given. The last dose of digifoline was given on September 28, and there was only one further short episode of tachycardia, on September 30.

Subsequently, she has been seen at regular intervals by her pediatrician. Characteristic eczema developed, but she has had no further difficulty referable to her heart. A faint systolic murmur was heard at some, but not at other, examinations. She has continued to have difficulty from eczema and later from asthma, but she has had no further episodes of tachycardia during the year and a half subsequent to the episodes mentioned.

CASE 4.—J. C., a female infant, was born by cesarean section on June 12, 1939. Her weight at birth was 8 pounds 4 ounces (3,742 Gm.). There were no postnatal disturbances. She progressed satisfactorily until the age of 2 weeks, when she began to vomit directly after nursing. She seemed somewhat pale when she was seen by her family physician, who prescribed iron medication. On July 1 she became pale and limp. The mother found her respirations difficult to count.

The following day, July 2, she was admitted to the Children's Hospital. She had a rapid heart rate and rapid respirations. Her color was fairly good, and she appeared to be in moderately good condition. No cardiac murmurs were heard. Her abdomen was distended, with moderate enlargement of the liver. The spleen was not palpable.

On the day of admission and the following night she had increasing respiratory difficulty and her color became poor. The next day, July 3, the heart rate was over 200 and a diagnosis of paroxysmal tachycardia was made. An electrocardiogram showed a rate of 280 (fig. 4). A roentgenogram showed moderate enlargement of the cardiac shadow, with a considerable amount of pulmonary congestion. Examination of the blood showed: hemoglobin content, 70 per cent; red cell count, 3,930,000 per cubic millimeter, and white cell count, 23,600 per cubic millimeter, with 68 per cent neutrophilic leukocytes. Her weight was 8¼ pounds (3,742 Gm.).

Digitalis therapy was started, with an initial dose of 0.1 Gm. of digifoline given intramuscularly, after which the pulse rate dropped promptly to normal. No more digitalis was given. The respiratory rate dropped from 120 to about 50. The temperature, which had fluctuated between 98 and 101 F., continued to show similar elevations during the next few days. Lumbar puncture yielded xanthochromic spinal fluid containing crenated red cells.

The baby progressed satisfactorily during the next week. At the age of 4 weeks there was recurrence of the rapid respirations and the cyanosis. She was admitted for the second time to the hospital, when the heart rate was thought to be about 300. On admission lumbar puncture again yielded a large amount of xanthochromic spinal fluid containing crenated red cells. The total protein content was 195 mg. per hundred cubic centimeters. After the lumbar puncture the tachycardia ceased, and she subsequently progressed satisfactorily and normally. She was last seen at the age of 6 months, having been perfectly well since the second discharge from the hospital.

CASE 5.—R. B., a male infant, was born normally at full term on Aug. 26, 1939. The weight at birth was 8 pounds 2 ounces (3,685 Gm.). There were no postnatal disturbances. Since the mother's milk was insufficient, he was given a usual

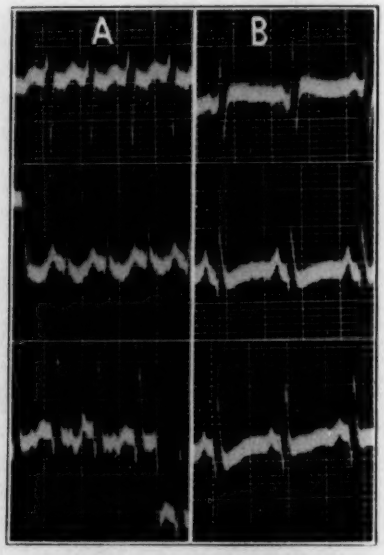

Fig. 4 (case 4).—*A*, July 3: paroxysmal tachycardia, supraventricular; right axis deviation. Rate 300. *B*, July 4: normal rhythm; axis normal for age; low T waves (following digitalis). Rate 150.

formula. He progressed satisfactorily until the age of 4 weeks, at which time he started refusing most of his feedings and vomiting. There was considerable dyspnea. When lying down he would cry, cough, choke and vomit; these symptoms were relieved by propping him up on pillows. On the following day the local physician who was caring for the baby called in the obstetrician, who advised a change in the formula and prescribed nose drops. These measures did not help.

On September 30 the baby's condition appeared critical and it was noted that the heart rate was over 250. He was grayish and cyanotic and had severe dyspnea. The heart was greatly enlarged. No cardiac murmurs and no rales were heard. The edge of the liver was felt at the level of the umbilicus (fig. 5). The tip of the spleen was palpable. There was moderate edema of the scrotum. A diagnosis of paroxysmal tachycardia with congestive failure was made. The baby was given

an initial dose of 0.1 Gm. of digalen intramuscularly and was then admitted to the Infants' Hospital. At the time of admission an electrocardiogram showed a rate of 270 (fig. 6). The heart appeared markedly enlarged on a roentgenogram (fig. 7 *A*), with a transverse diameter of 7.7 cm.; the internal diameter of the chest was 11.1 cm. There was considerable congestion in both lungs. A routine urinalysis gave normal results. The hemoglobin content was 75 per cent, and the red cell count was 3,640,000 per cubic millimeter. The white cell count on admission was 11,750 per cubic millimeter, with 85 per cent polymorphonuclear leukocytes. The following day the white cell count rose to 20,750 per cubic millimeter. The temperature was normal on admission but rose during the day to 102 F. His

Fig. 5 (case 5).—The edge of the liver and the spleen are marked to show the enlargement during the attack of tachycardia and the decrease in size with the return of the heart rate to normal.

weight was 8½ pounds (3,856 Gm.). More digitalis was given in the form of 0.2 Gm. of digifoline, in two doses of 0.1 Gm. each. Thus the total dose of digitalis preparations was 0.3 Gm. during twenty-four hours.

The following morning the pulse rate dropped to normal. The baby appeared greatly improved. The dyspnea stopped, and there was no further cyanosis. The edge of the liver had receded, and the spleen was no longer palpable. A second roentgenogram of the heart and lungs, taken on October 2, twenty-four hours after the rate had returned to normal, showed a striking change (fig. 7 *B*). The pulmonary congestion had disappeared, and the transverse diameter of the heart had decreased by almost 1 cm. The temperature and the respiratory rate also

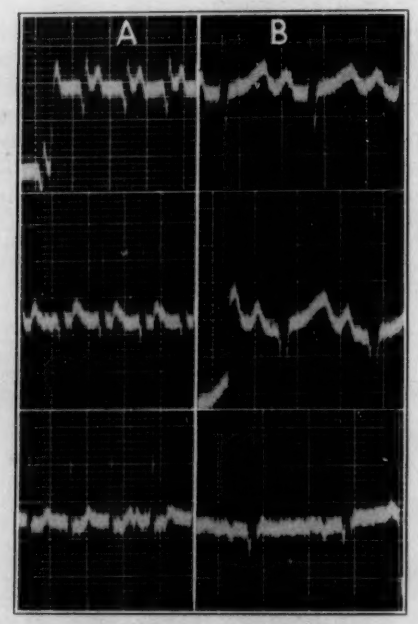

Fig. 6 (case 5).—*A*, September 30: paroxysmal tachycardia, supraventricular. Rate 260. *B*, November 27: normal; inverted P waves in lead III.

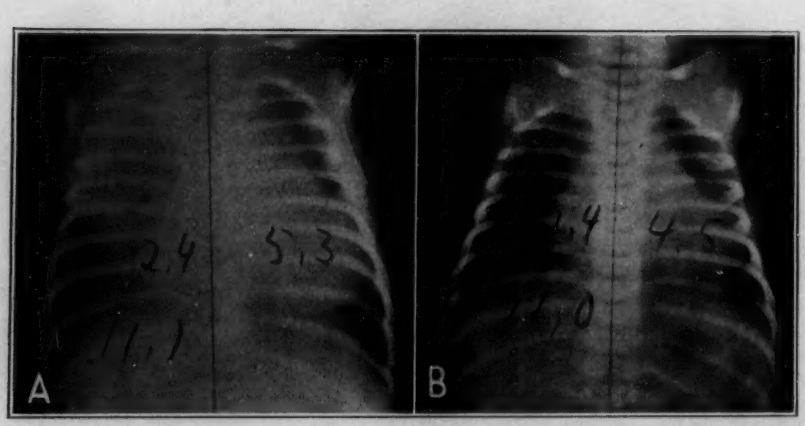

Fig. 7 (case 5).—Teleroentgenograms taken (*A*) during (Sept. 30, 1939) and (*B*) after (Oct. 2, 1939) the attack of tachycardia, showing the disappearance of pulmonary congestion and the decrease in the transverse diameter of the heart (from 7.8 to 6.9 cm.).

dropped to normal (fig. 8). No more digitalis was given, and there was no recurrence of tachycardia. The patient was last seen at the age of 6 months, at which time he was considered entirely normal.

CASE 6.—W. M., a male infant, was born normally, of healthy parents, on Sept. 26, 1939. The weight at birth was unknown. At the age of 11 days he weighed 5 pounds 5 ounces (2,140 Gm.). There were no immediate postnatal disturbances. The mother's milk was insufficient, so the baby was given a routine formula, with which he gained satisfactorily.

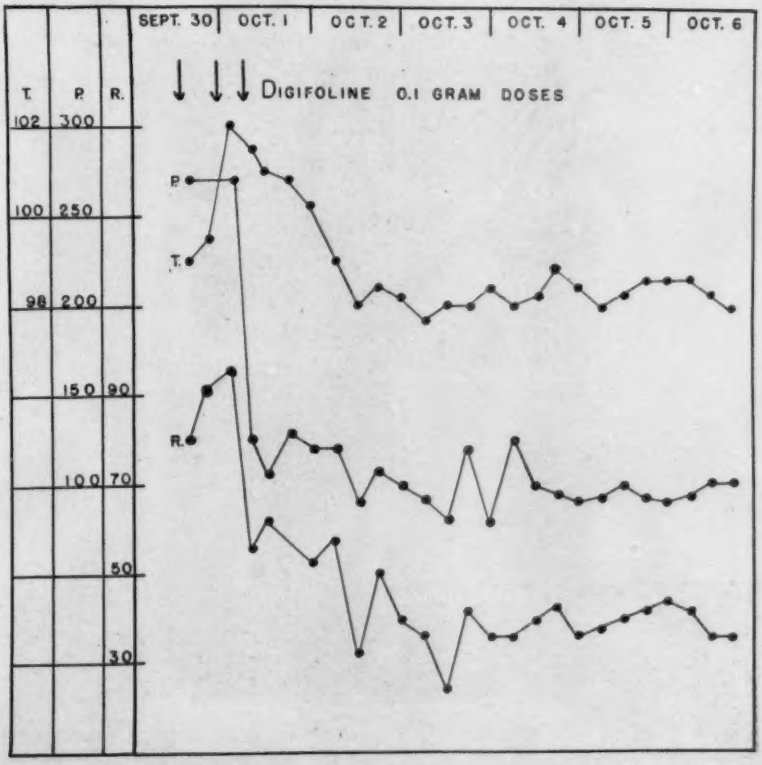

Fig. 8 (case 5).—Effect of digitalis on the temperature (*T*), the pulse rate (*P*) and the respiratory rate (*R*).

He was thought to be entirely normal until the age of 2½ weeks, when, on October 12, he started vomiting frequently after feedings. This continued for the next week. During this time the baby was not seen by any physician. On October 18, at the age of 3 weeks, he was seen by a social worker, who observed that the baby's color was poor and the heart rate rapid. On her advice the baby was brought to the hospital, on October 20, at which time the pulse rate was thought to be about 300.

His weight on admission was 6 pounds 14 ounces (3,118 Gm.). His color was ashen, with moderate cyanosis of his lips and extremities. The heart was moderately enlarged. There were no murmurs. The lungs were clear. The edge of the liver was palpated at the level of the umbilicus. The spleen was not felt.

There was no apparent edema. Fluoroscopic examination on admission showed moderate enlargement of the heart, with no visible cardiac pulsations. An electrocardiogram showed a rate of 290 (fig. 9). It was considered advisable by the resident staff to administer mecholyl chloride, and he was therefore given 5 mg. Four minutes after this dose an abrupt change took place in the condition of the baby, with profuse lacrimation, frothy salivation and constriction of the pupils. The baby voided and broke out into a cold sweat. Moist rales were heard throughout the chest. No heart sounds could be heard. Electrocardiographic tracings were obtained almost continuously. These showed first a period of ventricular fibrillation which was followed by widely spaced, weak ventricular contractions, one occurring about every one or two seconds. Eight minutes after the mecholyl

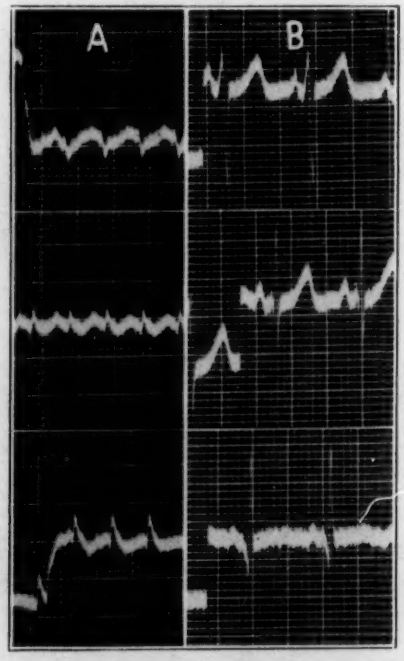

Fig. 9 (case 6).—*A*, Oct. 20, 1939: paroxysmal tachycardia, supraventricular, with aberrant ventricular responses, or even possibly ventricular tachycardia; low complexes in all leads; right axis deviation. Rate 290. *B*, Feb. 14, 1940: normal rhythm; right axis deviation. Rate 125.

was given, 1/500 grain (0.13 mg.) of atropine sulfate was injected intravenously. The systolic contractions began to increase and then broke into ventricular tachycardia, which was followed by a return to the original tachycardia. Digitalis therapy was then started, with an initial dose of 0.1 Gm. of digifoline. About seven hours later the heart rate returned to normal. Another dose of digifoline (0.05 Gm.) was given.

On October 23 there was another short attack of tachycardia. Digifoline (0.05 Gm.) was given again, after which the pulse rate immediately became normal and remained so.

No further attacks of tachycardia were observed clinically, but while an electrocardiogram was being taken in the clinic, at the age of 2 months, the rate again

rose to 190. He was seen again on December 6. His condition had been satisfactory during the interval, with a good gain in weight. There were no difficulties of which the mother was aware. An electrocardiogram taken at this time showed a rate shifting from 110 to 195, with right axis deviation (angle of 128 degrees). He was seen again on Jan. 17, 1940, when he was thought to be normal, and no electrocardiogram was taken. He was last seen on February 14. He had been well except for a minor infection of the upper respiratory tract. Another electrocardiogram showed a normal rate of 130, still with considerable right axis deviation. There had been no further episodes of tachycardia when he was last seen, at the age of 6 months.

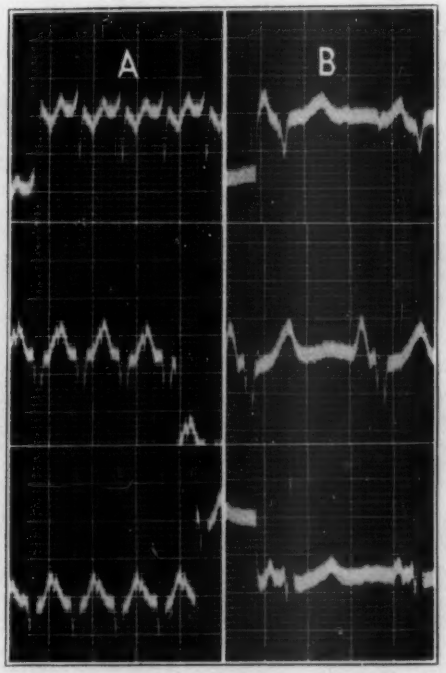

Fig. 10 (case 7).—*A*, November 26: paroxysmal tachycardia, auricular; right axis deviation. Rate 290. *B*, November 28: normal rhythm; abnormally high P waves in lead II; right axis deviation. Rate 100.

CASE 7.—M. B., a male infant, was born normally on April 22, 1939. There were no postnatal disturbances. His general development and his health were considered satisfactory until the age of 7 months, when he was seen by his family physician because of rapid breathing and rapid pulse rate. Because of this he was admitted to the Children's Hospital on November 26.

On admission his respirations were rapid, the rate being about 80. The pulse was too fast to count. No cardiac murmurs were heard. His liver was moderately enlarged. He weighed 18 pounds (8,165 Gm.). A routine urinalysis gave normal results except for a slight trace of albumin and acetone. The hemoglobin content was 86 per cent. The red cell count was 5,560,000 per cubic millimeter, and the white cell count, 29,400, with a normal differential count. An electrocardiogram (fig. 10) showed a rate of 305, with slight right axis deviation (angle of 105

degrees). A roentgenogram taken at the same time showed no enlargement of the heart, the transverse diameter being 7.2 cm. and the internal diameter of the chest 15 cm. The lungs appeared clear except for an area of dense cloudiness in the upper portion of the right lung, which was considered to be pneumonic infiltration.

In view of the roentgen observations on the chest and the finding of type XV pneumococci in moderate numbers in a culture of material from deep in the throat, the patient was given one dose of 0.25 Gm. of sulfapyridine (2-[para-aminobenzenesulfonamido] pyridine). Then digitalis therapy was started, with an initial dose of 0.1 Gm. given intramuscularly. He was given two more doses of the same amount, so that he received 0.3 Gm. of digitalis in twenty-four hours.

The following day the temperature, which had been 103 F., dropped to normal and remained so. The pulse rate dropped to 110, and the respiratory rate fell

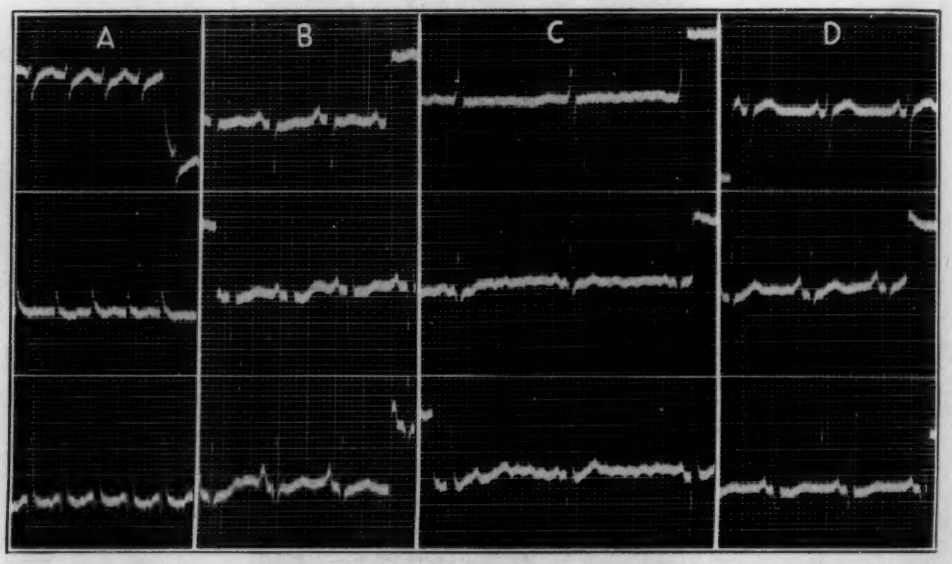

Fig. 11 (case 8).—*A*, February 21: paroxysmal tachycardia, supraventricular. Rate 270. *B*, February 23, 9:30 a. m.: normal rhythm; inverted T waves (following digitalis). Rate 150. *C*, February 23, 11:30 a. m.: auricular fibrillation. Rate 70. *D*, February 28: normal rhythm; right axis deviation. Rate 110.

from 85 to 30; both rates subsequently remained normal. The baby's general condition seemed greatly improved. A second roentgenogram, taken on the following day, November 28, showed no significant change in the area of pneumonia.

In view of the persistent roentgen evidence of pneumonia, sulfapyridine therapy was again instituted. The baby subsequently made a satisfactory convalescence. Another roentgen examination of the chest, on December 4, showed evidence of resolution of the area of pneumonia. The baby has not been seen since his discharge from the hospital, on Dec. 4, 1939.

CASE 8.—M. C., a female infant, was born normally, of healthy parents. Since the mother's milk was insufficient, a customary formula was given. The birth weight of 7 pounds 10 ounces (3,459 Gm.) was regained on the tenth day, and

during this time she was considered entirely normal. In a routine examination at the age of 10 days it was noted that her heart was beating rapidly. An electrocardiogram showed tachycardia, with a rate of 270. A roentgenogram showed some enlargement of the cardiac shadow. The lungs were considered to be clear. The following day she had moderate dyspnea and a general grayish color but no cyanosis. The heart rate was too fast to count. No cardiac murmurs were heard. The liver was enlarged, with the edge 3 cm. below the costal margin. The white cells numbered 14,200 per cubic millimeter of blood. A diagnosis of paroxysmal tachycardia was made, and the baby therefore was given a dose of digifoline (0.1 Gm.). In five hours the rate had dropped to normal but rose

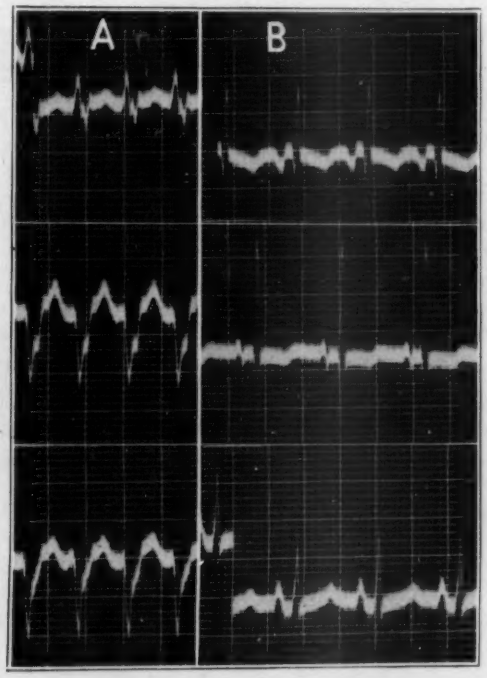

Fig. 12 (case 9).—*A*, August 28: paroxysmal tachycardia, auriculoventricular nodal; left axis deviation. Inverted P waves follow QRS in lead I and are superimposed on QRS in leads II and III. Rate 220. *B*, August 29: normal rhythm; P waves inverted in lead I, diphasic in lead II; T waves inverted in leads I and II; no axis deviation (following digitalis). Rate 145.

again the following day to over 200. A second dose of digifoline was then given (0.1 Gm.), after which the pulse rate dropped and then showed gross irregularities, which, as demonstrated by the electrocardiogram, were due to auricular fibrillation (fig. 11).

Digitalis was then discontinued, and the rhythm became regular. Two and three days later there were short paroxysms of tachycardia; so digitalis was again started (0.05 Gm. daily). There were no further attacks; digitalis was withdrawn gradually, and the baby had had no further difficulties at the age of 6 weeks. when she was last seen.

CASE 9.—B. C., a male infant, was born normally at full term. He was considered normal until the age of 13 days, when cyanosis was noticed by the nurse. His respirations became rapid, and he was immediately sent to the hospital, with a provisional diagnosis of pneumonia.

On physical examination he appeared to be in fairly good condition. The respirations were rapid, the rate being 80 to 100, but there was no cyanosis. The heart was pounding rapidly, with loud, unduly forceful sounds. The rate was judged to be 240. The edge of the liver was felt 2 to 3 cm. below the costal margin. There was no apparent edema.

A teleroentgenogram made on admission showed great enlargement of the heart, with pulmonary congestion but no pneumonia. An electrocardiogram showed paroxysmal tachycardia, with a rate of 220, with retrograde inverted P waves denoting an auriculoventricular nodal origin (fig. 12). His white cell count was 12,500 per cubic millimeter of blood. His weight was 8 pounds and 13 ounces (3,997 Gm.).

A dose of digifoline, 0.05 Gm., was given intramuscularly. Nine hours later, there having been no change in the pulse rate, a second dose of digifoline, 0.05 Gm., was given. During this interval the temperature had risen to 101 F. Seven hours after the second dose of digifoline the pulse rate dropped suddenly from 220 to 140. There was a more gradual decline in the respiratory rate. The baby made an uneventful recovery, with no recurrence of tachycardia during the next week, during which he was under observation in the hospital.

A second electrocardiogram, taken a few hours after the drop in pulse rate, showed a rate of 145. Teleroentgenograms showed marked decrease in both the size of the cardiac shadow and the amount of peribronchial congestion.

He has not been seen since discharge from the hospital, at the age of 3 weeks.

Dr. Dorothea Moore (case 3), Dr. Robert Ganz (cases 4 and 7), the staff of the Boston Lying-in Hospital (case 8) and Dr. Lewis W. Hill allowed me to consult with them in the care and study of their patients and permitted me to report these cases. Dr. Samuel A. Levine gave advice in the study of Dr. Moore's patient, and Dr. Paul D. White gave criticisms and help in this study.

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A SIMPLE METHOD FOR THE ISOLATION AND IDENTIFICATION OF MENINGOCOCCI AND GONOCOCCI

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An increased carbon dioxide tension has been employed for many years in the isolation of meningococci and gonococci. In 1918 Chapin [1] described this method for the cultivation of gonococci, and in the same year Cohen and Fleming [2] reported that there was a much better growth of meningococci when carbon dioxide was added in 10 per cent concentration. It is generally believed that these investigators probably thought that the improved growth of the organisms was due to the resultant decrease in oxygen tension, since this was the prevailing opinion at that time. The value of the method has been corroborated on numerous occasions, although there have been differences of opinion as to the factor primarily responsible. In addition to the decrease in oxygen tension, an increase in moisture and the production of a more favorable p_H have been considered. In 1924 Smith [3] found that carbon dioxide was essential for the growth of certain freshly isolated strains of Brucella abortus and that the other factors were only contributory. More recently, Valley and Rettger [4] and Gladstone and his associates [5] have demonstrated that carbon dioxide is essential for bacterial growth

Aided by a grant from the Fluid Research Fund of Yale University School of Medicine.

From the Department of Pediatrics, Yale University School of Medicine, and the Pediatric Service of the New Haven Hospital and Dispensary.

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3. Smith, T.: Some Cultural Characters of Bacillus Abortus (Bang) with Special Reference to CO_2 Requirements, J. Exper. Med. **40**:219 (Aug.) 1924.

4. Valley, G., and Rettger, L. F.: The Influence of Carbon Dioxide on Bacteria, J. Bact. **14**:101 (Aug.) 1927.

5. Gladstone, G. P.; Fildes, P., and Richardson, G. M.: Carbon Dioxide as an Essential Factor in the Growth of Bacteria, Brit. J. Exper. Path. **16**:335 (June) 1935.

in general, and McLeod and his co-workers [6] and Leahy and Carpenter [7] have stressed the importance of the gas in the cultivation of gonococci.

Thompson [8] in 1935 described a simple and inexpensive method of furnishing carbon dioxide for this purpose. Meningococci and gonococci were found to grow well on ordinary mediums when they were incubated in a glass jar containing 10 per cent carbon dioxide produced by mixing sodium bicarbonate and sulfuric acid. This method seemed to offer special advantages in a clinical laboratory, where material for culture from persons suspected of having meningococcic or gonococcic infection is not received regularly enough to warrant having available at all times a fresh supply of special medium or the purchasing of expensive equipment.

We have employed Thompson's method in the pediatric laboratory of New Haven Hospital for the past three years, and the purpose of this paper is to corroborate the practicability of this technic for the isolation of meningococci and gonococci and to extend its use to the further identification of these organisms by fermentation tests.

MATERIAL AND METHODS

Mediums.—A fresh beef heart infusion with 1 per cent neopeptone was the basic medium used in this laboratory. The blood agar plates used for the isolation of the organisms were made by adding 10 cc. of defibrinated rabbit's blood to a flask containing 200 cc. of melted infusion agar. The blood and agar were mixed, and the mixture was poured into sterile Petri dishes and allowed to solidify. The contents of one flask made about fifteen blood agar plates.

For the fermentation tests, blood agar plates containing dextrose, maltose and levulose were used. Five-tenths cubic centimeter of defibrinated rabbit's blood was added to a tube containing 10 cc. of melted infusion agar. The contents of the tube were mixed and poured into a sterile Petri dish containing 2 cc. of 10 per cent dextrose. An even distribution of blood agar and carbohydrate was obtained by gently tilting the dish back and forth while the contents were still liquid. Blood agar plates with maltose and levulose were made in the same manner.

Carbon Dioxide Jar.—The apparatus is shown in figure 1. It consisted of a round, flat-bottomed, 2.5 liter pyrex jar, a square cover with corked aperture and a container for reagents. It differed only in minor details from the apparatus used by Thompson. The container for reagents was fastened to the bottom of the jar with sealing wax. Petrolatum was used to seal the cover to the jar.

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7. Leahy, A. D., and Carpenter, C. M.: The Diagnosis of Gonococcal Infections by the Cultural Method, Am. J. Syph., Gonor. & Ven. Dis. **20**:347 (July) 1936.

8. Thompson, L.: A Simple Method of Supplying Carbon Dioxide in Jars for Bacteriologic Cultures, Am. J. Clin. Path. **5**:313 (July) 1935.

Sodium bicarbonate and sulfuric acid were the reagents used. The sodium bicarbonate solution was made by dissolving 84 Gm. of sodium bicarbonate in 1 liter of water. The sulfuric acid solution contained 20 cc. of concentrated sulfuric acid per 580 cc. of water. Equal amounts of each reagent were used, and 22.4 cc. of carbon dioxide was formed from each 1 cc. of sodium bicarbonate solution. An amount of each solution which was equal to 0.45 per cent of the volume of the jar furnished an atmosphere of about 10 per cent carbon dioxide.

Source of Material.—Most of the material for culture was obtained from patients in the pediatric isolation wards of New Haven Hospital. Bacteriologic studies are part of the routine examination of these patients, and cultures of material from persons suspected of having meningococcic or gonococcic infection were incubated in the carbon dioxide jar. Infants and children in the outpatient clinic and newborn infants in private homes who had purulent discharge from the eyes

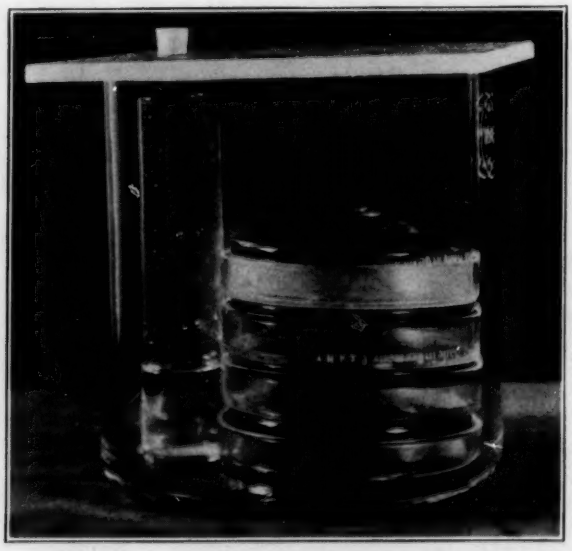

Fig. 1.—Carbon dioxide jar.

or the vagina furnished additional material for culture. When possible, material from the nose and throat was obtained for culture from healthy contacts of patients with meningococcic infections.

Isolation of Strains.—Purulent discharge from the eyes or the genital tract was obtained on a sterile cotton-tipped wooden applicator, was smeared over a small area near the edge of a blood agar plate and was streaked out with a platinum loop.

A 0.1 cc. sample of spinal fluid was placed on a blood agar plate with a sterile pipet and streaked in a similar manner.

Blood cultures were made by adding 5 to 7 cc. of the patient's blood to 50 cc. of infusion broth and by mixing 2 cc. of the citrated blood of the patient with 10 cc. of infusion agar to form a pour plate.

Material for culture was obtained from the nose by introducing a cotton-tipped wooden applicator into the nostrils until the nasopharyngeal wall was reached

and material from the throat, by touching both tonsils and the posterior portion of the pharynx. The material from the nose and that from the throat were streaked separately on blood agar plates.

The inoculated mediums were put in the carbon dioxide jar, the calculated amount of sodium bicarbonate solution was placed in the container for reagents and the jar was covered. An amount of sulfuric acid equal to that of the sodium bicarbonate solution was added through the hole in the cover by means of a pipet. The hole was closed with a cork, and the jar with its contents was incubated overnight at 37.5 C. Portions of colonies on the plates which resembled meningococci or gonococci were smeared on a glass slide, stained and examined microscopically. Blood cultures positive for these organisms were examined in a similar manner. If gram-negative diplococci were found, the organisms were further identified by their fermentation reactions.

Fermentation Tests.—Three blood agar plates, containing dextrose, maltose and levulose, respectively, were inoculated and incubated overnight in the carbon

TABLE 1.—*Source of Strains of Meningococci and Gonococci*

Source	Material for Culture						
	From Nose	From Throat	Spinal Fluid	Blood	From Eye	From Vagina	From Cervix Uteri
Patients with meningococcic meningitis (8)	2	2	8	1	..	..	..
Patients with meningococcic septicemia (2)	1	1	..	2	..	..	..
Carriers of meningococci (7)	4	5	..	..	..	..	..
Patients with gonococcic ophthalmia (4)	..	..	..	..	4	..	..
Patients with gonococcic vaginitis (3)	..	..	..	..	..	3	..
Patients with gonococcic cervicitis (1)	..	..	..	..	..	..	1

dioxide jar. One drop of 2 per cent bromthymol blue was placed on each of the plates in an area where colonies were present. Fermentation of the sugar was indicated by a change in the color of the indicator from dark blue to yellow.

RESULTS

Twenty-six strains of meningococci and 8 strains of gonococci have been isolated during the past three years from material brought to the pediatric laboratory. The source of the strains is shown in table 1. Seventeen of the strains of meningococci were recovered by culture of material from 10 patients with meningococcic infection; the remaining 9 were from cultures of material from 7 healthy carriers.

Meningococci and gonococci both grew out well within twenty-four hours and were recovered on the first culture of material from the local lesion. In 2 instances the organisms were not visible in a stained smear of the purulent exudate (spinal fluid from a child with meningococcic meningitis and discharge from the eye of a newborn infant with gonococcic conjunctivitis), but cultures were positive for them. The con-

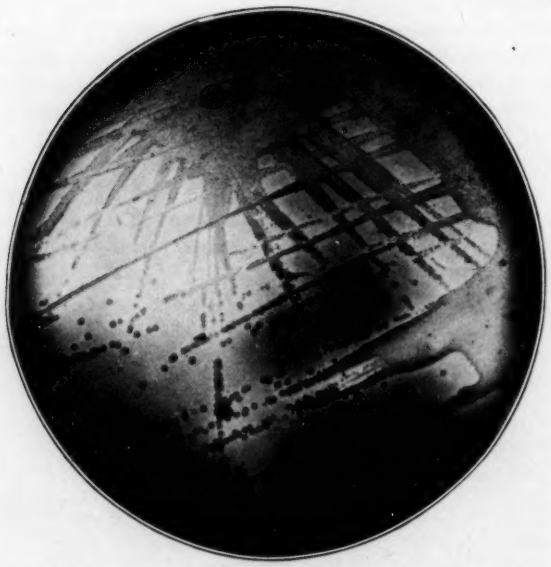

Fig. 2.—Colonies of meningococci in an eighteen hour culture of spinal fluid.

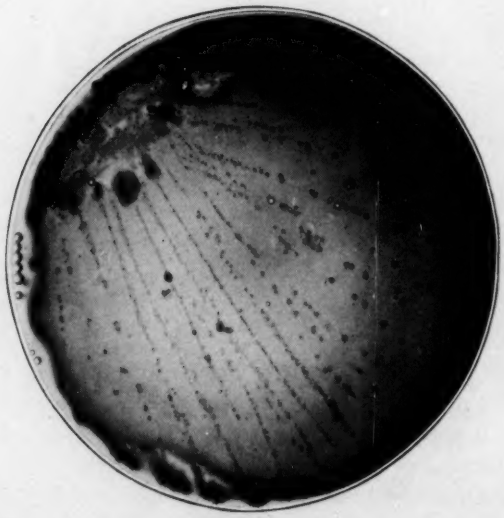

Fig. 3.—Colonies of gonococci predominating in a twenty hour culture of vaginal discharge.

verse was not encountered. Figures 2 and 3 are photographs of colonies on blood agar plates after incubation in the carbon dioxide jar.

All of the 34 strains of meningococci and gonococci gave characteristic fermentation reactions, as is shown in table 2, when they were cultured by this method on blood agar plates containing the differential carbohydrates. When fermentation occurred the change in the color of the indicator was sharp.

COMMENT

The carbon dioxide jar described by Thompson offers a practical method of isolating meningococci and gonococci on blood agar plates, and the simple addition of the differential carbohydrates to the blood agar permits satisfactory further identification of the organisms.

It should be mentioned that table 1 does not indicate the relative frequency with which meningococci may be cultured by this method from material from the upper respiratory tract of patients with meningococcic infections. The carbon dioxide jar was at first used routinely

TABLE 2.—*Results of Fermentation Tests*

Organism	Number of Strains	Sugar Used in Fermentation Tests *		
		Dextrose	Maltose	Levulose
Meningococcus	26	A	A	—
Gonococcus	8	A	—	—

* A signifies that acid was produced, and —, that no fermentation took place.

only for the isolation of the organisms from material from the local lesion (spinal fluid or blood). Cultures of material from the nose and throat of 7 of the 10 patients were incubated aerobically and failed to show colonies of meningococci. However, meningococci were recovered from cultures of material from both the nose and the throat when the material was incubated in the carbon dioxide jar.

Table 3 demonstrates the stimulating effect of the atmosphere of 10 per cent carbon dioxide furnished by this method on the growth of meningococci and gonococci. Two blood agar plates were inoculated with each of 15 specimens of material for culture from 9 patients. One of the plates was then incubated in the usual manner; the other was incubated in the carbon dioxide jar. The same specimen of material for culture was used for both plates. A 0.1 cc. specimen of well mixed spinal fluid was placed on each of the two plates and streaked out. The same cotton swab was used for inoculating each of the two plates with material from the nose, the throat and the eye. The plate to be incubated aerobically was inoculated first in order to be sure that it received at least as heavy an inoculum as the plate to be incubated in the carbon dioxide jar. Plates incubated in the carbon dioxide jar

were read at the end of twenty-four hours; plates incubated aerobically were ready at the end of twenty-four and of forty-eight hours.

Colonies of meningococci were present on 3 of the 15 plates incubated aerobically, while the remaining 12 plates were negative for meningococci or gonococci. Of the corresponding plates incubated in the carbon dioxide jar, 13 were positive for meningococci or gonococci and 2 failed to show colonies of either organism. It is of interest that the meningococci from the 2 healthy carriers grew well in the absence of increased carbon dioxide tension. This suggests that the organisms

TABLE 3.—*Effect of Ten per Cent Carbon Dioxide Atmosphere on the Growth of Meningococci and Gonococci*

Patient	Age, Years	Disease	Date of Culture	Material for Culture	Blood Agar Plate *	
					Aerobic	Carbon Dioxide Jar
V. N.	5	Meningococcic meningitis	1/ 4/38	From nose	—	+P
			1/ 4/38	From throat	—	+
			1/ 4/38	Spinal fluid	—	+
R. C.	6	Meningococcic meningitis	3/25/38	Spinal fluid	—	+
E. M.	6	Meningococcic meningitis	3/31/38	Spinal fluid	—	+
			4/ 2/38	Spinal fluid	—	+
S. S.	15	Meningococcus carrier	1/10/39	From nose	—	—
			1/16/39	From throat	+P	+P
P. E.	7	Meningococcus carrier	3/ 9/39	From nose	+P	+P
			3/ 9/39	From throat	—	—
K. E.	1	Meningococcic septicemia	3/24/39	From nose	—	+
E. G.	2	Meningococcic meningitis	5/ 8/39	From nose	+	+P
			5/ 8/39	From throat	—	+
A. D.	4 days	Gonococcic ophthalmia	9/18/37	From eye	—	+P
L. L.	7 days	Gonococcic ophthalmia	10/17/39	From eye	—	+P

* — signifies that no colonies of meningococci or gonococci were present in the culture; +, that colonies of these organisms were present, and +P, that colonies of these organisms predominated in a mixed culture, such as of material from the nose, the throat and the eye.

had become more resistant than usual and that the failure to demonstrate their presence in material from both the nose and the throat by culture with the aid of an atmosphere of 10 per cent carbon dioxide was due to their absence from the inoculum.

SUMMARY

Twenty-six strains of meningococci and 8 strains of gonococci were isolated in the pediatric laboratory during a three year period; the carbon dioxide jar of Thompson was used for the cultures. The organisms grew out well in twenty-four hours on blood agar plates and were recovered from material from all of the infected patients on the first culture. It was found that the simple addition of the differentiating carbohydrates to the blood agar afforded a satisfactory method for further identification of the organisms by fermentation tests.

BIG BABIES AND THEIR AFTER-HISTORY

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Big babies, like twins, are always of interest, not only to their mothers, who take pride in the new edition of the old stock, but to persons outside the family.

We define big babies as those who at birth weigh over 4,000 Gm. (8 pounds 13 ounces), the most commonly used definition in the literature. The frequency of birth of such large infants has been reported as varying all the way from 1 per hundred births in Tokyo to 15 per hundred in Esthonia. Such aspects of the subject of heavy birth weight as considerations on the biggest living babies on record, the frequency of heavy birth weights with reference to the distribution of all birth weights, the mortality of big babies (before and after birth) and the relation of heavy birth weight to disease (especially diabetes) will be elaborated elsewhere.

The purpose of this paper is to illuminate the question of the increase in weight normally to be expected for big babies during the first two years of life. The objective for the mother and for the physician is the optimum health of the baby, specifically, the optimum (not the highest) level of nutrition, and for this the most convenient criterion is body weight.

MATERIAL

There was available for study a series of infants who (1) had been weighed at birth by a physician, (2) were subsequently brought to a physician for systematic (usually monthly) follow-up and (3) were kept in the best of health. Of this group we took for study 6 girls and 4 boys weighing more than 8 pounds (3,629 Gm.) at birth, and for purposes of comparison we chose 2 healthy boys who weighed less than 8 pounds.

RESULTS

We compared the weights of the 12 children with the average weights, by age and sex, for children of American stock and discovered:

1. At birth none of the 12 babies was extremely heavy or extremely light; their weights at birth ranged from 148 to 68 per cent of the

The expense of this study was defrayed mainly by the Rockefeller Fluid Research Fund.

From the Medical Department of Stanford University School of Medicine and the Santa Barbara Clinic.

average birth weight, with a mean for the 10 big babies of 127 per cent, or 27 per cent over the average birth weight.

2. At the time of latest observation, which was at the average age of 5.3 years, the weights of the 10 big babies ranged from 129 to 95 per cent of the average weight for their ages, with a mean of 110 per cent. Of the 10 big babies, 2 at the time of latest observation actually weighed less than normal for their age and height; both were children of a diabetic mother. It may therefore be concluded that a big baby will continue to weigh more than the average child of its age, unless it is the offspring of a diabetic mother, in which case its weight will probably regress to (or even below) the average level.

Data on the weights of the 12 children are given in the table.

Data for Ten Babies Weighing More and for Two Weighing Less Than Eight Pounds at Birth

Infant	Sex	Birth Weight		Relation of Birth Weight to Average Birth Weight, per Cent*	Age, Years	Latest Weight Recorded, Kg.	Relation of Latest Weight Recorded to Average Weight for Age, per Cent
		Gm.	Lb.				
A. L.	F	4,050	8.9	123	5.2	21.9	106
M. P.	F	4,170	9.2	127	5.7	23.8	110
M. U.	F	3,760	8.3	115	3.4	18.14	113
M. K. F.	F	3,980	8.6	121	2.5	15.42	112
A. H.	F	4,030	8.9	123	3.5	16.33	95
C. H.	F	4,760	10.5	145	2.0	11.79	97
J. H. L.	M	4,750	10.5	136	2.5	16.10	110
R. B. L.	M	3,830	8.4	110	2.7	20.9	126
M. J. M.	M	5,190	11.4	148	6.5	33.11	129
A. M. G.	M	4,200	9.3	120	18.9	83.5	103
Mean	..	.....	...	...	5.3	....	110
K. O.	..	2,381	5.2	68	1.8	12.0	94
R. A. W.	..	3,430	7.6	98	2.6	13.6	101

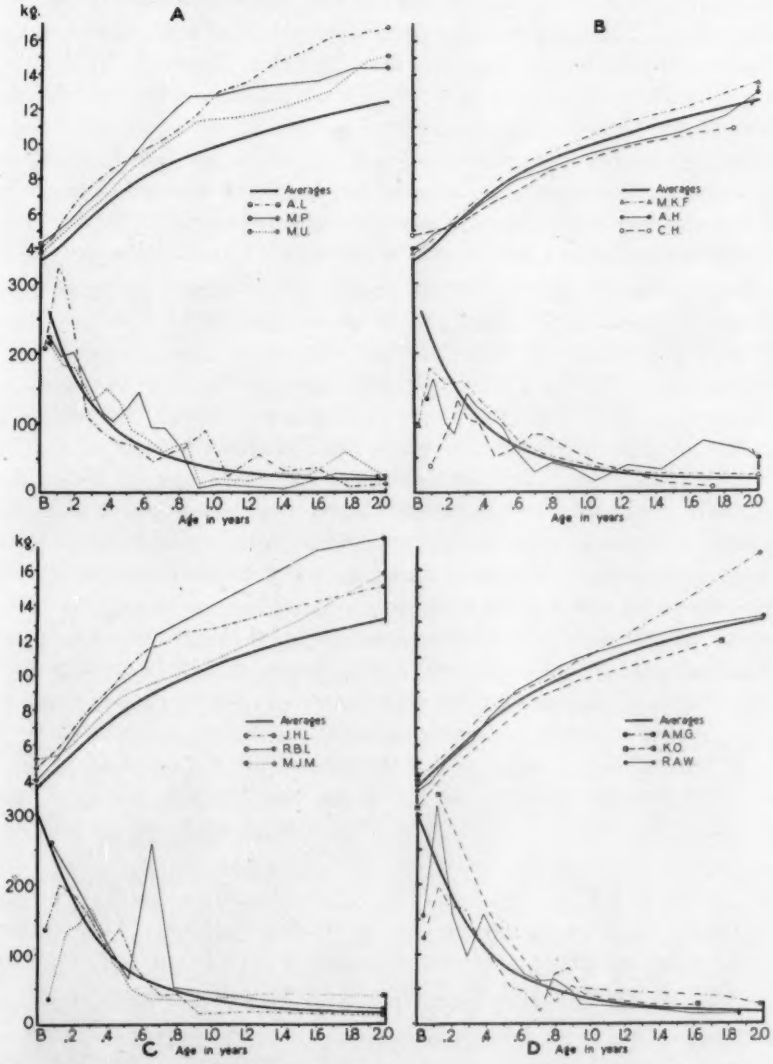
* Average birth weight for boys was taken as 3,497 Gm., and that for girls as 3,280 Gm.

In the chart the babies are grouped by sex, but otherwise the grouping is merely to minimize the confusing crossing of curves. Absolute weight is shown by the upper curve in each of the component parts of the chart, and the lower curve shows more clearly the changes in rate of weight increase, a refinement usually ignored but not unimportant. The scale for the rate of weight increase is the percentage instantaneous rate $\frac{1}{W}\frac{dW}{da} \times 100$, calculated with logarithms to the base *e*, as was suggested in the paper by Bayer and Gray.[1] (In this formula dW is the difference in weight during the change in age, da, and W is the weight at any given instant.) The heavy line curves show average weights for sex and age, based on a series of about 100 West Coast girls and boys, all of whom were kept under observation for considerable periods,[2]

1. Bayer, L. M., and Gray, H.: Pituitary Dwarfs, California & West. Med. **47**:228 (Oct.) 1937.

2. Faber, H. K., and Gray, H.: Unpublished data.

Averaging the weights masked the fluctuations ordinarily occurring in individual curves, a phenomenon which is usually present but is often ignored. It is not surprising, therefore, that the individual rate curves reveal several remarkable features.



Weight curves for 10 babies weighing more and for 2 weighing less than 3,629 Gm. at birth. The upper curve of *A*, *B*, *C* and *D* represents absolute weight; the lower curve of each section represents the rate of weight increase. The average weight curves were constructed with data for 100 West Coast girls and boys.

Absolute Weight.—The absolute weight curves show that as a rule babies keep their relative weights during the first two years of infancy

with considerably more uniformity than has been found for children of school age. The exceptions to be noted are:

(1) The absolute weight curves for the 2 girls A. H. and C. H., shown in *B*, receded gradually to the average level, so that after they were about 3 months of age the curves ran fairly uniformly below the average line. These 2 girls were sisters, daughters of a diabetic mother. Women with diabetes are known to bear big babies unusually frequently, but it is not known whether as a rule the weight curves for their babies behave as did those for these 2 sisters.

(2) The absolute weight curve for R. A. W., a boy, which is shown in *D*, followed the average curve until he was about 4 months old, after which it ran tolerably uniformly above the average curve. The explanation may lie in the fact that he was weaned at 4 months of age.

Rate of Weight Increase.—The percentage or relative instantaneous rate curves appear at first glance to be too confusing to bother with, but this need not be so. It should be remembered that accelerations and decelerations in the rate of weight increase occur at different ages in different persons. Therefore, one could hardly expect the peaks of acceleration in the curves for the groups of 3 children in *A*, *B*, *C* and *D* to occur exactly in a vertical line above the same age point on the horizontal time scale. Nevertheless, the peaks can reasonably be expected to occur at approximately the same age. To test the validity of this expectation, a tabulation was made of the age of each of the 12 babies at which any notable peak occurred. The results may be summarized as follows: The instantaneous rate for weight increase is at birth about 300 per cent per year; it decreases rapidly according to a power formula, until at the age of 2 years it is about 10 per cent per year. There are, however, notable accelerations during this period; some of our babies had as many as five peaks and all of them had at least two. The six ages at which the spurts are most likely to occur and the number of the 12 babies who showed a peak at each are as follows:

Age in weeks.....	6	17	33	44	65	88
Number of babies.....	7	8	3	7	2	4

The causes of these spurts are by no means obvious. The earliest spurts, those occurring at about 1½ and 4 months of age, may be attributed to weaning and the increased liberalization of the diet.

CONCLUSIONS

Babies big at birth tend to continue to weigh more than the average children of their age, at least during the first two years of life.

Notable spurts in the rate of weight increase, which in general rapidly declined, were shown by all of 12 infants at least twice during this period.

Dr. Francis E. Howard drew the charts, and Miss Sylvia Lowe made many calculations, the more significant of which, condensed, are included in this paper.

SUPERVISION OF CHILDREN IN CONTACT WITH TUBERCULOSIS

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The supervision of contacts has been generally accepted for a long time as a basic principle in the control of tuberculosis. Unfortunately, the term contact has rarely been exactly defined, and programs have paid little attention to the varying requirements of the supervision of contacts at different ages and under different conditions. This has been particularly true in respect to children, who make up a large part of contact case loads. Within recent years, however, a reorientation to the problem of tuberculosis in children in general has occurred. This has manifested itself in an attitude of skepticism in regard to the value of open air classes, summer camps and preventoriums and has led in some instances to the closing of these institutions. The foundation for this point of view has been furnished by numerous studies of tuberculous infection, morbidity and mortality in children, which have uniformly shown the striking decrease which has occurred in the prevalence of tuberculous conditions in children in recent years and the infrequency of cases of serious disease in this age group at present. Without reviewing the voluminous literature on this subject, I should like simply to point out that in 1939 in the entire city of New York, with a population of 7,347,000, only 118 persons less than 10 years of age died of all forms of tuberculosis, and of these 77 were children under the age of 3 years. Three and one-tenth per cent of all persons dying of tuberculosis were children under 10 years of age.

The problem of tuberculosis in child contacts has proved less susceptible of analysis, however. Much of the difficulty has resulted from the failure to distinguish between children exposed to presumably infectious tuberculosis and those exposed to presumably noninfectious forms of the disease, although studies such as those made in Philadelphia by Opie, McPhedran and Putnam [1] and in Tennessee by Stewart, Gass, Gauld and Puffer [2] have shown striking differences in both the rate of

From the Bureau of Tuberculosis, Department of Health, New York City.

1. Opie, E. L.; McPhedran, F. M., and Putnam, P.: The Fate of Persons in Contact with Tuberculosis: The Exogenous Infection of Children and Adults, Am. J. Hyg. **22**:644, 1935.

2. Stewart, H. C.; Gass, R. S.; Gauld, R. L., and Puffer, R. R.: Tuberculosis Studies in Tennessee, Am. J. Hyg. **26**:526, 1937.

infection and the morbidity in the two groups of children. Another factor of great significance which has not been stressed sufficiently is the latent period and the consequent relative immunity of children between the ages of 3 and 10 years.

Prior to October 1938 the policy of the bureau of tuberculosis of the department of health of New York city, as given in its manual "Administration of Clinics," was to supervise all persons exposed to a patient with active tuberculosis, irrespective of age, at frequent intervals over long periods. The criteria for the activity of the disease in the source of infections were those of the National Tuberculosis Association, as given in "Diagnostic Standards." Children under 5 years of age were followed until 7 years of age if contact with the source of infection had ceased and into young adult life (25 years) if they were still exposed to a source of infection or to a person with a recently quiescent or arrested lesion. All children up to 16 years of age were routinely given tuberculin tests at the time of admission to the clinic. Roentgenograms were made of positive reactors, and negative reactors still exposed to a source of infection were retested every six months. Programs of this general character are still the common practice among agencies engaged in the control of tuberculosis.

About October 1938 it was decided to review the entire subject of the examination and supervision of children in the district diagnostic clinics of New York city. The first six months of 1938 were chosen for study. During this period 27,078 examinations of children under the age of 15 years were performed. These examinations were made on 12,081 persons, 4,919 of whom had not been seen previously in a health department clinic. It is impossible to state what proportion of these children were below 10 and what proportion were between 10 and 15 years of age, since all persons under 15 years of age were classified as children in the records. It is probably safe to assume, however, on the basis of population estimates and observations in clinic practice, that just as many, or more, children under 10 years as between 10 and 15 years of age were examined. The principal results of this study are shown in table 1.

The striking feature of this analysis is the infrequency with which cases of chronic pulmonary tuberculosis were noted among preadolescent children. The 2 cases occurred in a 9 year old white girl contact and a 7 year old Puerto Rican girl contact, and the infection was discovered at the time of the patients' first examination in the clinic. In the entire group of children less than 10 years of age under supervision in the district clinics of the department of health, not a single case of the reinfection type of tuberculosis was detected in the course of periodic revisits.

By way of contrast, in the older group, children 10 to 15 years of age, 14 children with chronic pulmonary tuberculosis of the reinfection type were observed. Eight of these were girls and 6 boys. Six children were white, 5 Negro, 2 Puerto Rican and 1 Asiatic. One child was 10 years of age, 2 each were 11 and 12, 6 were 14 and 3 were 15. All but 2 of the infections were discovered at the time of the patients' first visit to the clinic.

Unfortunately, it was not possible to determine the incidence of active primary tuberculosis among children in this study. At the time the examinations were made, primary lesions, irrespective of activity, were included under a single heading in the reports.

As a result of this study and the clinical experience of my associates and myself, the policies of supervision of children in the clinics were radically altered. The term "contact" was confined to persons intimately exposed to a patient with open pulmonary tuberculosis during

TABLE 1.—*Prevalence of Cases of Chronic Pulmonary Tuberculosis Among Children Examined in Clinics of New York City Department of Health, January to June 1938*

Age Group, Yr.	Total Number of Cases	Minimal	Moderately Advanced	Far Advanced	Discovered on		History of Contact	
					First Visit	Periodic Revisit	Present	Absent
0-10	2	2	..	..	2	..	2	..
10-15	14	10	3	1	12	2	8	6
Total	16	12	3	1	14	2	10	6

the preceding two years. A patient with open tuberculosis was defined either as one with positive sputum or roentgenologic evidence of cavity or as one with active tuberculosis who had been delinquent in attendance at the clinic for six months or longer and whose present status was therefore not known. All children in association with patients with tuberculosis were given an initial roentgenographic examination without preliminary sorting by means of tuberculin tests. White children under 12 years of age and Negro or Puerto Rican children under 10 years of age whose roentgenograms showed no evidence of a pathologic condition of the parenchyma were discharged from further supervision, even in the presence of continuing exposure to a source of infection. Children over these ages who were classified as contacts in accordance with the foregoing definition were supervised through periodic roentgen examinations, which are to be continued to the age of 25 years. Children in whom symptoms referable to the respiratory tract developed at any time were encouraged to return promptly. These policies have been in operation in all of the diagnostic clinics of the department since October 1938.

In April 1940 it was decided to analyze the experience with children again in the light of this new scheme of supervision of contacts. During the first three months of 1940, 5,278 examinations were made on 4,854 children under the age of 15 years, 2,253 of whom had not been seen previously in the clinics. These figures represent a decrease of more than 54 per cent in the number of visits and of more than 34 per cent in the number of persons seen, as compared with the figures for the corresponding period in 1938. The number of new persons seen in the two periods has remained relatively constant. The results of this study are summarized in table 2.

The 3 cases of chronic pulmonary tuberculosis among children under the age of 10 years occurred in female contacts, an 8 year old Negress and 2 white girls aged 8 and 10 years, respectively. Two of the girls

TABLE 2.—*Prevalence of Cases of Active Tuberculosis Among Children Examined in Clinics of New York City Department of Health, January to March 1940*

Age Group, Yr.	Total Number of Cases	Chronic Pulmonary Tuberculosis					Active Primary Tuberculosis	Miliary Tuberculosis	History of Contact		Diagnosed on		Patient Known to Have Tuberculosis on Admission
		Total	Minimal	Moderately Advanced	Far Advanced	Diagnosis Questionable			Present	Absent	First Visit	Periodic Revisit	
0-10	22	3*	..	2	..	..	17	2	17	5	19	..	3
10-15	23	20	10	7	1	2	3	..	7	16	18	5	..
Total	45	23*	10	9	1	2	20	2	24	21	37	5	3

* Includes 1 case in which the patient received artificial pneumothorax.

were known to have tuberculosis when first seen in the clinic, and the 8 year old white girl had a cavity in the lower lobe of the right lung which closed within three weeks, without treatment. Positive sputum was not obtained, and the diagnosis has not been bacteriologically confirmed as yet. The 17 patients with active primary tuberculosis included 8 boys and 9 girls. Nine children were white and 8 Negro. Four children were 1 year of age; 5, 2 years; 4, 3 years, and 1 each, 4, 7, 9 and 10 years old. For 1 patient the diagnosis had been made previously, and the child was known to have tuberculosis at the time of first examination in the clinic. Miliary tuberculosis was found in a white boy and a Negro girl, both in their second year of life. Of the entire group of 22 children under 10 years of age with active tuberculosis, a history of contact as previously defined was obtained for 17 and was absent for 5. Nineteen of the lesions were noted at the time of the children's first visit to the clinic, and 3 children were known to have tuberculosis at the time of their first examination in the clinic.

Twenty-three of the children 10 to 15 years of age were found to have active tuberculosis. Twenty of these had chronic pulmonary tuberculosis of the reinfection type, and 3 had active primary tuberculosis. Of the 20 children with the reinfection type of tuberculosis, 10 were boys and an equal number were girls. Eight were white; 10, Negro, and 2, Puerto Rican. The age distribution of the children was as follows: 3 were 12 years of age; 4, 13; 8, 14 and 5, 15. Ten of the lesions were minimal, 7 moderately advanced and 1 far advanced. In 2 instances the nature of the lesion is still in question. Thirteen children have already been admitted to a hospital, and 3 are on the waiting list for admission. One has refused hospitalization, and 3 are under clinic supervision. The 3 children with active primary tuberculosis were a Negro boy aged 12, a Negro girl aged 13 and a white boy aged 14. All 3 children have been hospitalized. Of the entire group of 23 patients, a history of contact was obtained for 7 and was absent for 16.

SUMMARY AND CONCLUSIONS

Certain definite conclusions stand out as a result of these two studies. The most important is that chronic pulmonary tuberculosis of the reinfection type rarely occurs among preadolescent children. In more than 32,000 examinations of almost 17,000 children, over 7,000 of whom were seen for the first time, only 5 cases of the reinfection type of tuberculosis were found among children under 10 years of age. In 2 of the 5 cases the diagnosis had been previously made, and in 1 other case the diagnosis is still in question. Among an equal or a smaller number of children 10 to 15 years of age, 34 cases of chronic pulmonary tuberculosis were discovered.

Another significant conclusion to be drawn is that almost all of the cases of tuberculosis in child contacts are found at the time of the first examination. In 51 of the 58 cases of tuberculosis this was true. The proportion of cases found on revisit in cases found on first visit during 1938, when periodic supervision of children was the routine practice, was 12.5 per cent, a figure which is not significantly higher than the 11.9 per cent for 1940, when children under 10 years of age were not being followed up. On neither occasion was a single case of chronic pulmonary tuberculosis of the reinfection type found in a child under 10 years of age as result of periodic supervision.

The final conclusion is that too much dependence should not be placed on securing a history of contact for children in a large city like New York. Such a history was obtained in only 34 of the 61 cases of tuberculosis, or in 55.7 per cent. In 27 cases, or 44.3 per cent, no history of contact could be elicited. Every member of the families of 16 of the patients in these 27 cases who might be a source of infection has been examined, and no cases of infectious tuberculosis have been

found. Thus, in more than 59 per cent of the cases the negative history of contact has been confirmed by complete examination of the members of the patients' families. During the two periods of study, 69.1 per cent of all the children were examined as contacts, and 55.7 per cent of the cases of active tuberculosis were found in this group. Almost half of the cases were discovered among children referred to the clinic for reasons other than contact and would have been missed in any program based primarily on the examination of contacts.

With these observations as a basis, the present program for the examination and supervision of children as outlined in the clinic manual of the bureau of tuberculosis of New York city has been evolved. All children in association with persons with pulmonary tuberculosis are given an initial roentgen examination. For those under 3 years of age, this examination is accompanied by a tuberculin test. Infants exposed to persons with open pulmonary tuberculosis, as previously defined, are retested and given roentgen examination every six months up to the third year of life. Infants not in contact with infectious tuberculosis and all children between 3 and 10 years of age who show no evidence of a pathologic condition of the parenchyma are dropped from further supervision. Supervision of all children who have been recently exposed to persons with open tuberculosis or who have a history of particularly heavy exposure earlier in childhood is resumed at the age of 10 years. By means of periodic roentgen examination supervision of all such persons is to be continued to the age of 25 years. Children with pulmonary symptoms are, of course, examined at any time. The experience of my associates and myself clearly indicates that a program of this nature eliminates many unproductive examinations of children and results in the discovery of almost all of the significant cases of tuberculosis present in this age group.

THE DIFFERENTIAL LEUKOCYTE COUNT ASSOCIATED WITH HOOKWORM INFECTION

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Although there is ample evidence to support the widespread belief that eosinophilia occurs in cases of hookworm infection, there is equally valid evidence that infections with this parasite may occur without any increase in the number of eosinophils in the peripheral circulation. The most striking instances of eosinophilia have been associated with acute infections. Ashford, Payne and Payne [1] reported percentages of eosinophils ranging from 62 to 91 in cases of acute massive infections with the European (Old World) hookworm, Ancylostoma duodenale, in previously well nourished, normal white children and adults in Puerto Rico. These patients were effectively treated with hexylresorcinol, and within a year after infection the eosinophil counts had dropped to as low as 6 per cent and in no case were above 33 per cent. Likewise, Boycott and Haldane [2] reported percentages of eosinophils ranging from 17 to 72 for English miners with relatively recent infections with A. duodenale. In a later publication, Boycott [3] noted that the increase in eosinophils caused by infection with A. duodenale is greater than that hitherto reported for infections with Necator americanus. While suggesting that perhaps infection with A. duodenale causes a greater

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This work was supported by a grant from the Samuel S. Fels Fund.

1. Ashford, B. K.; Payne, G. C., and Payne, F. K.: Acute Uncinariasis from Massive Infestation and Its Implications, J. A. M. A. **101**:843-847 (Sept. 9) 1933; The Larval Phase of Uncinariasis, Puerto Rico J. Pub. Health & Trop. Med. **9**: 97-153, 1933.

2. Boycott, A. E., and Haldane, J. S.: An Outbreak of Ankylostomiasis in England, J. Hyg. **3**:95-136, 1903.

3. Boycott, A. E.: Further Observations on the Diagnosis of Ankylostoma Infection with Special Reference to the Examination of the Blood, J. Hyg. **4**:437-479, 1904.

increase in eosinophils than does infection with N. americanus, he also stressed the fact that in his own series of cases of infection with A. duodenale the highest eosinophil counts were associated with the recent and less severe infections.

Oba [4] reported that the eosinophil count reached a peak of 29 to 37 per cent at the end of two months in cases of experimentally produced infections with A. duodenale in man, whereas in those produced with N. americanus a peak of only 13 to 15 per cent was reached in the same period. In both instances the eosinophilia decreased within six months. Boycott [5] reported on an infection with A. duodenale produced experimentally by ingestion of the infective material in which the percentage of eosinophils rose to 40 in forty-eight days. This rise occurred before eggs appeared in the feces. Similarly, in another case, in which the infection was acquired through the skin, the eosinophil count rose to 36 per cent in forty-eight days, eggs appeared in the feces in fifty days and the number of eosinophils continued to increase and reached a level of 45 per cent in fifty-two days. Unfortunately, the blood picture was not studied throughout the remainder of the infection.

In early studies on hookworm in Puerto Rico, Ashford and Igaravidez [6] reported that the average percentage of eosinophils in 61 cases of infections with N. americanus was 10.9, the extremes being 0.8 and 27.6. These workers suggested that eosinophilia is marked at some stage of hookworm infection but that the percentage of eosinophils may not be high throughout the course of the infection. They concluded that the eosinophil count is likely to be high for those patients who have harbored the infection for only a short time and low for those who have suffered a long, debilitating infection. They presented evidence showing that the removal of worms may induce eosinophilia in the latter type of patient. For the entire series for which data were tabulated the percentage of eosinophils after treatment averaged 13.7, with extremes of 0.8 and 35.6, as compared with the average percentage before treatment of 10.9.

In infections with Ancylostoma caninum experimentally produced in dogs, Sarles,[6a] in 1929, failed to demonstrate any marked eosinophilia,

4. Oba, T.: On the Morphological Changes of Blood in Infection with Ancylostoma Duodenale and Necator Americanus, Especially on Eosinophilia in These Cases, Taiwan Igakkai Zasshi, 1928, no. 278, p. 36.

5. Boycott, A. E.: Ankylostoma Infection (Milroy Lecture), Lancet **1**:783-790, 1911.

6. Ashford, B. K., and Igaravidez, P. G.: Uncinariasis (Hookworm Disease) in Puerto Rico, Senate Document 808, 1911, pp. 1-135.

6a. Sarles, M. P.: Studies of Blood Changes Occurring in Young and Old Dogs During Cutaneous and Oral Infection with Dog Hookworm, Ancylostoma Caninum, Am. J. Hyg. **10**:693-704, 1929.

but he did note a slight increase in these cells during the second and third weeks. On the other hand, Landsberg and Foster,[6b] in 1937, noted a rise in the percentages of eosinophils in most of their dogs with experimentally produced infections, yet they were unable to correlate this rise with any stage of the infection.

Since there are relatively few data available on the differential leukocyte counts in the cases of mild, chronic infection with N. americanus which are so numerous now in the southern states, we obtained such data for a representative group of children in the course of our studies on reticulocyte counts and hemoglobin levels.[7]

MATERIAL AND METHODS

Blood smears were obtained for 121 rural white school children in Sampson County, N. C., who had submitted fecal specimens for examination. The smears were stained with Wright's stain, and 200 cells were counted, under oil immersion, as they were observed in parallel fields across the slide. These studies were conducted on children from essentially nonmalarious districts. However, because of McVail's [8] suggestion that a concurrent infection with malaria may suppress eosinophilia in cases of hookworm infection, thick smears were made for examination for malarial parasites. At least 250 fields were examined for the parasites, under oil immersion, and in no case were any discovered.

In addition to the random sample of school children, we also made differential leukocyte counts for both the children and the adults of 5 families with pronounced anemia which Dr. Floyd Johnson, director of the health department of Columbus County, N. C., had under observation.

RESULTS

The average percentage of polymorphonuclear eosinophils for the 53 children infected with hookworm was 11.7, whereas for the 68 worm-free children the percentage of eosinophils was only 6.6 (table 1). Furthermore, the 29 more heavily infected children had, on the average, a higher percentage of eosinophils (13.0) than the 18 lightly infected children (9.3). However, none of them could be said to be very heavily infected and none of them had marked anemia, so that the higher percentage of eosinophils in the more heavily infected patients cannot be interpreted as being contrary to the suggestion of Ashford and Igaravidez [6] that the eosinophilia disappears or is decreased in cases of long-standing, debilitating hookworm disease.

6b. Landsberg, J. W., and Foster, A. O.: The White Cell Picture in Hookworm Disease of Dogs, Am. J. Hyg. **25**:141-149, 1937.

7. Brown, H. W., and Otto, G. F.: Haemoglobin and Reticulocyte Studies on Hookworm and Malaria Infected Children, Am. J. Hyg. (Sect. D) **33**:22-29, 1941.

8. McVail, J. B.: The Blood Count in Ankylostomiasis: A Warning, Indian M. Gaz. **57**:366-367, 1922.

The average figures mask some interesting individual variations which are brought out in table 2. Twenty-nine of the 68 children whose examinations were negative for hookworm had eosinophil percentages of less than 5, whereas there were only 6 children with such low eosinophil percentages among those infected with hookworm. As might be anticipated, the ratio was reversed for the higher eosinophil percentages; only 5 children classed as worm free had more than 15

TABLE 1.—*Differential Leukocyte Counts for Children With and Without Hookworm Infection*

	Number Examined	Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes	Immature Cells
Children with infection:							
Children who passed an average of 1,250 eggs per cc. of feces * and had approximately 50 worms	29	45.6	13.0	0.5	39.8	1.0	0.1
Children who passed fewer than 100 eggs per cc. of feces † and had approximately 4 worms	18	42.3	9.3	0.7	46.7	0.9	0.1
Total ‡	53	44.6	11.7	0.6	42.0	1.0	0.1
Children without infection	68	45.9	6.6	0.4	45.9	1.1	0.1

* Examination by both the Lane and the Stoll method was positive for hookworm.
† Examination by the Lane method was positive but by the Stoll method was negative for hookworm.
‡ Includes 6 children for whom examination by the Lane method was positive for hookworm but for whom no Stoll examination was carried out.

TABLE 2.—*Eosinophil Counts for Children With and Without Hookworm Infection*

	Percentage of Eosinophils															
							Above 15									
	0	1	2	3	4	5-14	16	17	18	19	20	23	24	26	27	44	Total
Children with infection	0	0	3	1	2	35	2	0	2	1	0	0	3	1	2	1	53
Children without infection	3	6	7	5	8	34	0	1	1	0	1	1	1	0	0	0	68
Total	3	6	10	6	10	69	2	1	3	1	1	1	4	1	2	1	121

per cent of eosinophils, whereas 12 of the infected children had percentages of from 16 to 44. Thus, as would be expected, consideration of the extremes of the individual eosinophil percentages supports the validity of the average figure, but it also verifies the fact that eosinophilia may be absent from infected persons and may be present to a marked degree in persons who pass no hookworm eggs in the feces. Furthermore, there was no correlation between the occurrence of marked eosinophilia and the intensity of infection, although the figures for the average percentage of eosinophils (table 1) suggest a direct correlation. It is interesting to note that the highest percentage of eosinophils (44) occurred in a child who passed only 200 eggs per cubic centimeter of feces, that is, who harbored approximately 8 or 10 hookworms.

Of interest are the percentages of eosinophils found for the members of 5 families with pronounced anemia (table 3). All of the members examined, both children and adults, of 4 of these families were infected. None of the 5 children examined in family 1 were infected. In this apparently worm-free family the percentages of eosinophils ranged from 0 to 7, with an average of 4.0. In the 4 infected families the degree of eosinophilia did not seem to be correlated with the intensity of infection but appeared rather to be influenced by a familial factor. Thus, the 6 children in family 2 who were examined had eosinophil percentages ranging from 5 to 11, with an average of 7.3; the 4 children in family 3 who

TABLE 3.—*Eosinophil Counts for Members of Five Families with Severe Anemia*

Family	Age of Subject, Years	Sex	Number of Hookworm Eggs per Cc. of Feces	Estimated Number of Hookworms	Hemoglobin, Gm. per 100 Cc. of Blood	Percentage of Eosinophils
1	10	F	0	0	11.7	0
	8	F	0	0	10.5	1
	6	F	0	0	10.7	5
	3	F	0	0	9.3	7
	2	M	0	0	8.0	7
2	12	M	8,100	324	4.3	9
	10	M	2,400	96	9.2	11
	4	F	4,200	168	9.0	6
	1	F	9,200	368	4.9	5
	15	M	6,600	264	5.5	5
	3	M	8,000	320	6.2	8
3	14	F	800	32	7.7	6
	4	M	800	32	10.8	4
	7	M	2,000	80	3.5	2
	35	F	8,400	336	6.6	3
4	11	F	2,600	104	6.5	10
	15	F	7,600	304	9.1	10
	50	F	32,300	1,292	7.0	11
5	12	M	31,000	1,240	3.5	16
	45	F	1,800	72	9.2	22
	11	F	2,400	96	6.7	28
	55	M	18,800	752	4.1	13

were examined had eosinophil percentages of 2 to 6, with an average of 3.8; the 3 children in family 4 who were examined had eosinophil percentages of 10, 10 and 11; the 4 children examined in family 5, however, had eosinophil percentages of 13, 16, 22 and 28. The data from study of these families suggest a familial relation in the eosinophilic response to infection, and it is possible that this is a reflection of a familial allergy.

While there may be a genetic factor in the eosinophilic response to hookworm infection, it seems to us that the degree of eosinophilia in these families, as well as in the children for whom data are summarized in tables 1 and 2, may be related to the stage and the duration of the infection. Ashford, Payne and Payne [1] have presented evidence that a high degree of eosinophilia is associated with acute or recent infec-

tions. Unfortunately, the methods available do not permit any attempt to estimate, even roughly, the duration of any given infection or how recently new worms may have been acquired. It is evident that hookworm infection is not static, and conditions which permit 30 to 40 per cent of the school children to become infected must provide an ample diversity in the history of infection. Thus, even some of those persons examined in whose feces no eggs were found may have acquired an infection in the preceding two or three weeks and thus have been harboring only sexually immature worms. It was during this early, or larval, stage of infection that Ashford, Payne and Payne [1] found such high degrees of eosinophilia in patients in Puerto Rico, and Boycott [5] noted percentages of eosinophils above 30 before eggs could be found in the feces of 2 subjects experimentally infected with A. duodenale. Likewise, others of the children may have received medication at home and have recently lost their worms. Either explanation might account for the occurrence of eosinophilia in children in whose feces no eggs could be found.

Since the members of family 1 were not passing any hookworm eggs, the chances of any member's having acquired an infection recently must be materially less than if a local source of infection had been present in the family. Hence it is not surprising that the percentages of eosinophils in the members of this family should be less than in the random sample of worm-free school children (tables 1 and 2).

Those persons who were discharging eggs in their feces may have harbored the infection for a long period, or they may have recently acquired it. Since the opportunity to acquire new infections is largely localized within family units (Otto, Cort and Keller [9]), it is not surprising that the degree of eosinophilia should bear a family relation. The postulate that eosinophilia is induced early in the course of infection but may disappear in cases of chronic disease would satisfactorily explain our results, although our data may hardly be said to confirm the postulate.

Although eosinophilia seems to be induced early in the course of hookworm infection, it does not necessarily follow that the addition of new worms will again induce eosinophilia. In this connection, however, Bachman and Rodriguez-Molina [10] have presented graphs suggesting that eosinophilia occurred when they attempted to superinfect

9. Otto, G. F.; Cort, W. W., and Keller, A. E.: Environmental Studies on Families in Tennessee Infected with Ascaris Trichuris, and Hookworm, Am. J. Hyg. **14**:156-193, 1931.

10. Bachman, G. W., and Rodriguez-Molina, R.: Resistance to Infestation with Trichinella Spiralis in Hogs: The Eosinophilic and Precipitin Response, Am. J. Hyg. **18**:266-294, 1933.

pigs with larvae of Trichinella spiralis. The percentage of eosinophils after an attempted superinfection was never as high as that induced by the first infection.

Aside from the polymorphonuclear eosinophils, the lymphocytes appear to be slightly more numerous than normal, at the expense of polymorphonuclear or neutrophil leukocytes, in children both with and without worms. In fact, the percentages of these two types of cells were almost identical with those in children of the same age groups who were suffering from malnutrition because of inadequate food intake (Otto [11]). This lends further support to our suggestion [7] that these children are probably suffering from the effects of an inadequate and unbalanced diet as well as from those of infection with hookworm.

CONCLUSIONS

It appears likely that eosinophilia occurs at some stage of infection with N. americanus, as has been suggested by Ashford and Igaravidez. On the other hand, eosinophilia is not always present in such infections, and in regions where the infection is common a high percentage of eosinophils may be present in patients whose feces contain no hookworm eggs. Our data may be explained by Ashford's suggestion that eosinophilia is associated with acute or recent infections, although they can hardly be said to verify his suggestion.

Dr. Floyd Johnson and Dr. J. H. Williams, directors of the health departments of Columbus County and of Sampson County, respectively, and their staffs of nurses gave assistance in this study.

11. Otto, G. F.: Blood Studies on Trichuris-Infested and Worm-Free Children in Louisiana, Am. J. Trop. Med. **15**:693-704, 1935.

REGULATION OF BODY TEMPERATURE DURING SLEEP

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NEW YORK

In a previous paper [1] it was shown that during an afternoon nap children exhibit a fall in rectal temperature which takes place usually in association with an initial rise and subsequent decline in the cutaneous temperature and the rate of evaporation of water from the body. At the time a way was being sought to eliminate error in measuring the basal rate of insensible perspiration over short periods. It was, however, pointed out that the oscillations in cutaneous temperature and in evaporation during sleep appear to result from a thermoregulatory process which operates in association with the lowering of the temperature of the body. The present paper will present new data and offer an amplified discussion of the experiments in so far as they bear on the regulation of body temperature.

METHODS

The same technic was used as previously. Data are presented from 96 experiments on 9 normal children from 5 months to 4 years of age. During the course of an afternoon nap simultaneous measurements were made of the insensible loss of weight, the temperature of the skin at selected points and the rectal temperature. The environmental conditions varied greatly from day to day, but during any one experimental period the relative humidity fluctuated 2 to 5 points, and the room temperature, 0.5 to 1 degree C. (0.9 to 1.8 degree F.).

Each child received breakfast in his own home. He was brought to the clinic in the morning, two or three hours before the beginning of the observations, and was allowed to play in a room a few degrees cooler than the experimental room. He was given a glass of milk at 11:30 a. m. At some time between 1 and 3 p. m., when he appeared sleepy, he was brought to the experimental room, was unclothed and was placed on the pan of the balance. Observations on the rectal and the cutaneous temperature were begun at once. Weighings were begun as soon as the quietness induced by sleep permitted, which was from fifteen minutes to an hour or more after the child was placed on the balance. Observations were continued until the experiment was terminated either by the child's awakening or by his urinating.

Cutaneous temperature was measured by a radiometer accurate to 0.2 degree C. It was made by Dr. James D. Hardy, of the Russell Sage Institute of Pathology.

From the Normal Child Development Study of the Department of Pediatrics, Columbia University College of Physicians and Surgeons and the Babies Hospital.

1. Day, R.: The Effect of Sleep on Insensible Perspiration in Infants and Children, Am. J. Dis. Child. **58**:82 (July) 1939.

Rectal temperature was measured concurrently by a continuously recording nickel resistance thermometer,[2] which was accurate to 0.05 degree C. The cable to the rectal element was so fixed to the pan of the balance and to a rigid support that the accuracy of the balance was not diminished.

The balance was made by Sartorius and possessed a sensitivity of 20 mg. with a load of 20 Kg. It was equipped with a damper, so that the weight loss could be measured during periods as short as two to five minutes with an error not greater than ± 5 per cent. Readings for consecutive short periods were combined so that a curve of the rate of weight loss could be drawn for comparison with the curves for the cutaneous and rectal temperatures. In order to reduce air currents, the entire balance was enclosed in a housing except for an opening in front of the subject, measuring 100 by 70 cm.

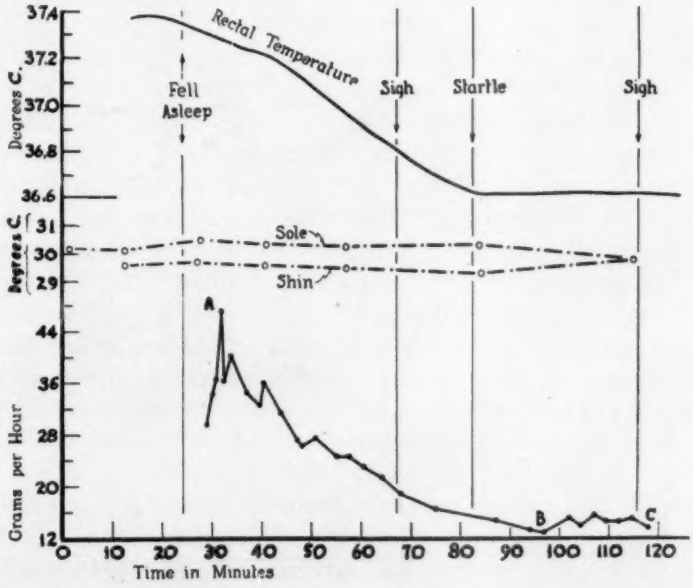

Chart 1.—Changes in the rectal and the cutaneous temperature and in the rate of weight loss during an afternoon nap. The subject, A. N., weighed 13.68 Kg. The room temperature was 79.5 F., and the relative humidity was 48 per cent.

It was considered that the fluctuations in rate of weight loss represented changes in rate of evaporation from the skin. Changes in the rate of respiration were slight and could not have accounted for the large changes which were observed in the rate of weight loss. It was also assumed that any changes in the output of carbon dioxide would be both slight and constant in direction and amount.

RESULTS

Rectal Temperature.—With the onset of sleep the rectal temperature always falls, the mean decrease being 0.55 degree C. (0.99 F.). When it ceases to fall it does so rather suddenly, so that there is an angulation

2. The thermometer was manufactured by Leeds and Northup.

in the curve traced by the recording thermometer. At this moment the child always stirs in his sleep. A typical curve showing the angulation is reproduced in chart 1. Thus, in the rectal temperature curve alone there is evidence of a regulatory process. If the fall were the result solely of a decrease in heat production, the temperature would approach its new level gradually instead of suddenly. Furthermore, the amount of the fall would probably be greater. The temperature of the body was usually about 11 degrees C. (51.8 F.) above that of the room. As was mentioned in the previous paper,[1] most observers place the decrease in heat production during sleep above 10 per cent. Even a 10 per cent

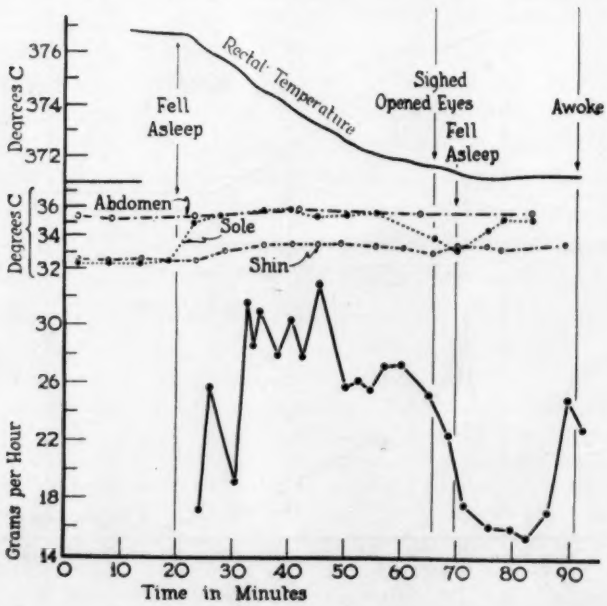

Chart 2.—Changes in the rectal and the cutaneous temperature and in the rate of weight loss during an afternoon nap. The room temperature (82 F.) was slightly higher, and the relative humidity (29.5 per cent), somewhat lower than in the experiment illustrated by chart 1. The chart shows the inhibition of sweating when the rectal temperature was becoming level. The subject, A. P., weighed 12.7 Kg.

decrease would cause a fall of around 1.1 degrees C. (1.98 degrees F.) (10 per cent of the difference between body and room temperature) if some regulatory mechanism did not impede heat loss.

Evaporation.—The curve in chart 1 showing the rate of loss of weight is of a type frequently encountered. The rate is seen to rise as sleep begins and then to fall during the period of declining temperature, later becoming level. Further oscillations occur occasionally (see chart 2

and the previous paper [1]). The rate at point *A* (in chart 1) is the maximum rate, and that at *B* is the minimum rate. The "basal rate," as the term is used in this paper, is the average rate during a period, such as that between *B* and *C* in chart 1, when the rectal temperature is no longer falling, the child is quietly sleeping and the rate of weight loss is constant. In experiments such as that illustrated by chart 2, in which oscillations continue to take place, the minimum rate is used as the best approximation of the basal rate. In those experiments in which a long steady state was maintained, it was noted that the values for the minimum rate and for the basal rate were closely similar.

Relation of Environment to Evaporation.—The constant association of a high or rising initial rate of weight loss with a falling rectal temperature suggests that the increased loss by evaporation actually represents a physiologic effort to lower body temperature. If this is so, in a warm room, where maximum cutaneuos temperature is already present before sleep and further rises cannot take place, one would expect the initial peak in evaporation to be higher than under cooler environmental conditions. If, on the other hand, the high initial rate is a sympathetic phenomenon incidental to sleep and is not related to the fall in rectal temperature, one would not expect conditions of increased warmth or humidity to be associated with a higher initial peak.

The data support the former conception. In some of the experiments in a very warm and humid room, visible perspiration appeared on the brow, the neck and the shoulders during the first part of the nap and disappeared later. This environmental effect is also reflected in the table, which presents the results of two groups of experiments selected from the series in order to contrast the effect of extremes in environment. In one group the measurements were made in a warm and humid room; experiments were arbitrarily placed in this group when the room temperature was 27.2 C. (81 F.) or above and the relative humidity was 45 per cent or above. The other group of experiments were carried out in a dry, cool room; experiments arbitrarily placed in this group were those in which the temperature was 24.4 C. (76 F.) or below and the relative humidity was 41 per cent or less. An index of the fall in the rate of weight loss (F_w) was used in comparing the results of the two groups of experiments. This value is a measure of the excess initial evaporation. It is the maximum rate (represented by point *A* in chart 1) divided by the minimum rate (point *B*) and multiplied by 100. The fall from the peak rather than the rise to the peak was used for this index, for two reasons: First, as a result of restlessness before and just at the onset of sleep, the ascending part of the curve was technically difficult to obtain accurately; second, by using a fall in rate to measure the excess initial evaporation, it cannot be objected that the index

results from increased evaporation associated with the child's entry into the warm experimental room or to the assumption of a horizontal position. In the warm, humid environment this value averaged 239.5, whereas under the cool, dry conditions it averaged 149.7; the ratio of the difference between these values to the standard error of the difference is 5.6 (P is less than 0.001, which is highly significant).

Differences Between the Index of Fall in the Rate of Weight Loss (F_w) and the Rectal Temperature Under Two Sets of Conditions

Subject	Room Temperature F.	Room Temperature C.	Relative Humidity, per Cent	Fall in Rate of Weight Loss (F_w)	Rectal Temperature: Fall F.	Fall C.	Initial F.	Initial C.	Lowest F.	Lowest C.
Warm, Humid Environment										
T. H.	83	28.34	69	250	1	0.56	99	37.23	98	36.67
S. D.	84.5	29.12	52	350	1	0.56	98.8	37.11	97.8	36.56
E. F.	81.5	27.5	72	255	0.6	0.33	99.3	37.39	98.7	37.06
B. M.	81.5	27.5	48	232	1.35	0.75	99.85	37.69	98.5	36.95
B. M.	85	29.45	60	214	0.5	0.28	98.5	36.95	98	36.67
A. N.	81	27.22	45	260	1.4	0.78	98.6	37	97.2	36.23
P. A.	82.5	28.06	50	254	0.8	0.45	98.6	37	97.8	36.56
P. A.	82	27.78	53	197	1	0.56	99.4	37.45	98.4	36.9
P. B.	81	27.22	66	181	0.7	0.39	99.4	37.45	98.7	37.06
J. S.	84	28.89	84	220	0.75	0.42	99.2	37.33	98.45	36.92
J. B.	86	30	64	224	0.45	0.25	98.65	37.03	98.2	36.78
J. B.	84	28.89	50	236	0.4	0.22	97.8	36.56	97.4	36.34
C. D.	86	30	46	240	1	0.56	99	37.23	98	36.67
Mean	83.2	28.45	58	239.5	0.84	0.47	98.89	37.16	98.068	36.72
Cool, Dry Environment										
T. H.	76	24.45	21	115	1.1	0.61	99.4	37.45	98.3	36.84
B. M.	76	24.45	34	163	1.2	0.67	98.8	37.11	97.6	36.45
B. M.	74.5	23.61	25	140	1.25	0.7	99.05	37.25	97.8	36.56
A. N.	76	24.45	38	144	1.4	0.78	100	37.78	98.6	37
A. N.	72.5	22.5	38	163	1.7	0.95	98.7	37.06	97	36.11
P. A.	73	22.78	35	114	1.25	0.7	99.1	37.28	97.85	36.59
P. A.	74.5	23.61	30	121	0.6	0.33	99.3	37.39	98.7	37.06
P. B.	75	23.89	30	183	0.8	0.45	99	37.23	98.2	36.78
P. B.	73	22.78	33	128	1.5	0.83	99.5	37.5	98	36.67
J. B.	72	22.22	38	231	0.8	0.45	99.45	37.48	98.65	37.03
J. S.	75	23.89	41	145	0.95	0.53	99.15	37.31	98.2	36.78
Mean	74.3	23.5	33	149.7	1.14	0.63	99.22	37.35	98.08	36.71

That the value of F_w is significantly affected by environment can be shown also by examination of the data from all 96 experiments.[3] The association of F_w with relative humidity is expressed by a value for chi

3. In making this analysis, as well as some others in this paper, a simple method was chosen rather than the conventional procedures of correlation, because, in the absence of any reason for assuming that the associations were linear, the greater labor of computing r's was not justified. When the relation between two series of corresponding values (such as between F_w and the environment) was to be tested, each series was divided arbitrarily at the median into two groups; that is, the graph of chart 3 *A*, for instance, was divided into right and left and upper and lower halves, each half containing 48 points. The resulting four quadrants were treated as a 2 × 2 contingency table, the figure assigned to each cell being

square of 8.7 and is highly significant; the association of F_w with room temperature, however, is only of borderline significance (chi square = 4.2). Because it cannot be concluded that both temperature and humidity affect F_w unless these two factors were essentially unassociated during the experiments, the test was applied to the relation between

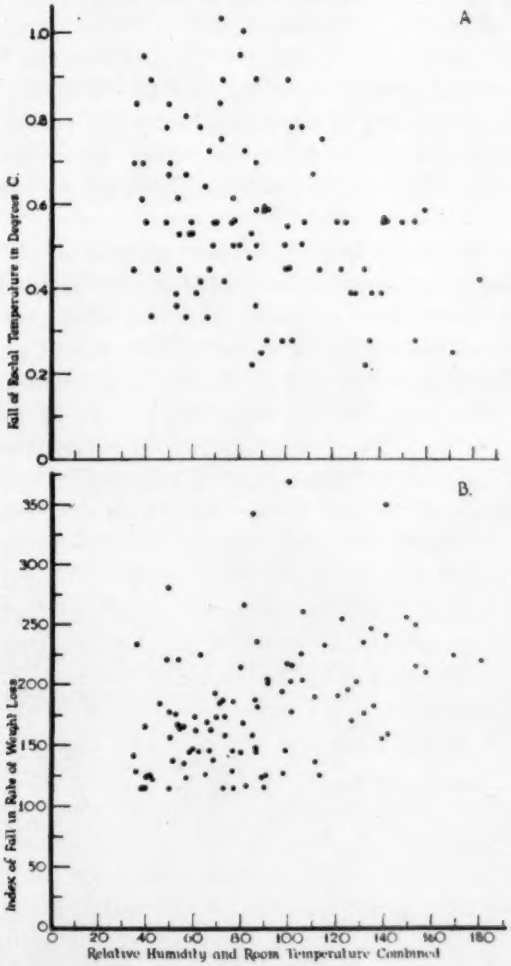

Chart 3.—The effect of environment (*A*) on the fall in rectal temperature and (*B*) on the index of fall in rate of weight loss (F_w).

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the number of points falling within the corresponding quadrant. Significance of association was then tested by the method of chi square. Such a test can be interpreted as evidence of borderline significance ($P = 0.05$) when chi square reaches a value of 3.8 and as evidence of high significance ($P = 0.01$) when the value is greater than 6.6.

temperature and humidity. The resulting value of 3.3 for chi square fails to disclose significant association and allows the belief that both factors contribute to the effect on F_w.

The combined effect of temperature and humidity on F_w can be tested statistically and can be shown graphically (chart 3) by a simple expedient. Both temperature and humidity were reduced to a common scale of units by assigning 0 to the lowest and 100 to the highest observed value of each and appropriate numbers from 0 to 100 for the intervening values. These new unit values for temperature and humidity were then added, so that the higher the resultant sum, the more difficult were the environmental conditions for body cooling. The association of these new values with F_w (chart 3) is expressed by a value for chi square of 13.5.

The preceding paragraph has been concerned with the effect on F_w of differences in room temperature and humidity. A significant positive relation was demonstrated. It becomes of interest, therefore, to determine to what extent this effect is due to the physical action of the environment and to what extent to a physiologic reaction of the body to the environment. For example, the value of F_w could be increased by sweating during the period of maximum rate of evaporation or by a depression of the basal or minimum rates of evaporation as a result of a high vapor pressure of the air. In extremely warm and humid rooms visible perspiration was present throughout an experiment. Under slightly cooler conditions it was noted only during the initial phases of the sleeping period, that is, during the period of maximum rates. The presence of sweating during the periods of basal or minimum rates of evaporation was, in these more comfortable zones, impossible to detect by palpation. Examination of the data, however, for basal rates from serial observations on the same children indicated that environmental limits could be selected above which the basal rates exhibited wide divergence from the trends established by other observations; such divergences were assumed to be the result of activity of the sweat glands. In order to determine the effect of environment on the true basal "insensible" perspiration, experiments were excluded which were performed in environments in which the divergences mentioned were noted to occur. Twenty of the 96 experiments were excluded because the room temperature was above 27.8 C. (82 F.), because the relative humidity was above 70 per cent or because a room temperature above 26.7 C. (80 F.) was associated with a relative humidity above 59 per cent. The results of the remaining 76 experiments were examined for association between the basal rate and the environmental factors. Between humidity and the basal rate of weight loss per kilogram of body weight there was a significant negative coefficient of correlation;

the value with its standard error was -0.548 ± 0.092. Just such a result would be expected if the vapor pressure of the atmosphere could act on the evaporation from the body according to physical laws without the intervention of active sweating. Between temperature and the basal rate there was a positive correlation near the borderline of statistical significance ($r = +0.28 \pm 0.14$). Treatment of the maximum rate in the same way did not reveal any significant correlation with either temperature or humidity. The failure of the fall of maximum rate to parallel that of the basal rate with rising humidity in this zone of environmental conditions strongly suggests the presence of sweat, even though none was visible or palpable.

In contrast to the results of this analysis of the maximum and basal rates of evaporation in those experiments in which the room was not very hot or humid are the results of the two small groups of experiments performed under widely differing environmental conditions which were used in the first analysis of F_w, namely, those carried out in the warm, humid room and those performed under the cold, dry conditions. It was found that the reason for the high values obtained for F_w in the experiments performed in the warm and humid room lay in a significant elevation of the maximum rate, associated with only a slight elevation of the basal or minimum rates, which was of borderline significance. The basal rate under the conditions of warmth and humidity was not lower than when the environment was cool and dry, as it would have been had not some factor (probably sweating) intervened to disturb the relation between humidity and insensible evaporation which was demonstrated under the less extreme conditions.

The behavior of F_w can be summarized in the following way: There is a continuous tendency for F_w to rise as the environmental conditions change in the direction which makes it more difficult to lose heat. At the lower end of the environmental scale increases in humidity are associated with decreases in the basal rate, while the maximum rate is relatively unaffected. In the higher regions of the scale the maximum rate increases rapidly with a rise in either the temperature or the humidity.

The decrease in the basal rate of evaporation with a rise in the humidity in the regions of moderate temperature is in agreement with the work of Wiley and Newburgh.[4]

Inhibition of Sweating.—It seemed surprising, in view of the sudden leveling off of the rectal temperature after thirty to forty-five minutes of sleep, that the figures for the rate of evaporation did not show a similar

4. Wiley, F. H., and Newburgh, L. H.: The Relationship Between the Environment and the Basal Insensible Loss of Weight, J. Clin. Investigation **10**: 689, 1931.

sudden change at this apparently critical point. Possibly evaporation has become purely passive by the time this moment arrives, so that even if there is inhibition of sweating at this time, it is not reflected in the figures. An experiment was performed to test this hypothesis (chart 4). Just before the expected time of leveling off of the rectal temperature, gentle radiant heat from an electric element was directed at the subject. The rate of evaporation was greatly increased as a result. However, when the subject stirred slightly, as was usual, at, or just before, the achievement of a level temperature, there occurred a sudden marked decrease in the rate of weight loss, even though the radiant heat was

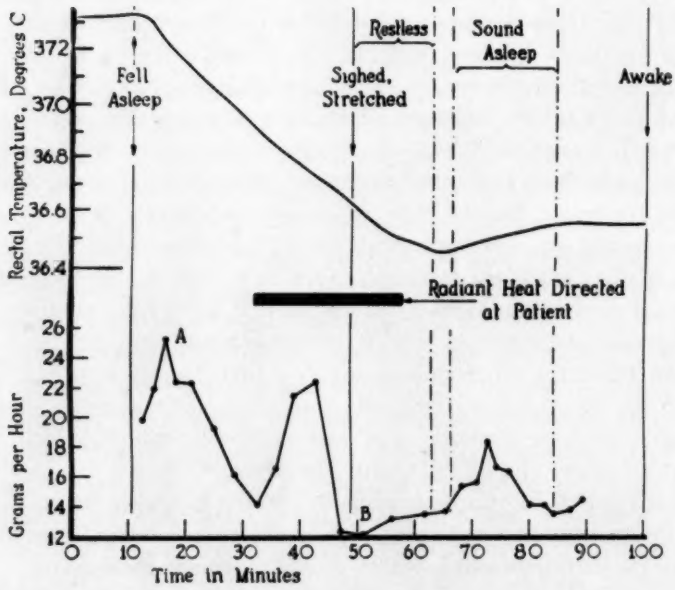

Chart 4.—Graph in the case of A. N., showing the inhibition of sweating induced by radiant heat shortly before the rectal temperature became level. The room temperature was 76 F. and the relative humidity was 41 per cent. The subject was the same as in chart 1.

continued. This drop in the rate was not permanent and in different experiments lasted from five minutes or less to ten minutes or more. These results suggest that there is a sudden inhibition of any sweating that may be going on at the moment of achievement of a level rectal temperature. A similar sudden decrease in evaporation was sometimes noted in warm and humid rooms, even without the use of radiant heat (chart 2).

These decreases in evaporation at the time when the rectal temperature ceases to fall present an interesting contrast to the increases noted during the early moments of the period during which the rectal temper-

ature falls. They demonstrate the purposive nature of the mechanisms which, by controlling heat loss, regulate the fall in body temperature that occurs in sleep.

Effect of Environment and Sleep on Cutaneous Temperature.—If the rate of evaporation is evidence of the working of purposive mechanisms during sleep, it is reasonable to look for parallel changes in cutaneous temperature. At the start it can be argued either that changes in cutaneous temperature are thermoregulatory or that they are not. Analysis of the effect of room temperature on the changes should aid in deciding which of the alternatives is the more likely. The sole is a singularly satisfactory area for recording drifts in cutaneous temperature. Fluctuations in its temperature, although in these experiments they were directionally the same as those of other sites,[5] possess the

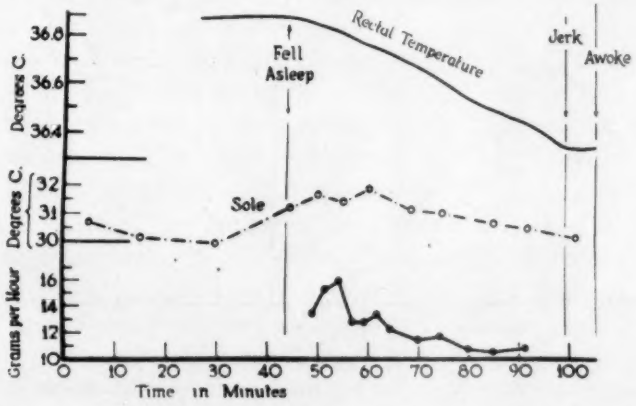

Chart 5.—Fluctuations in the rectal and the cutaneous temperature and the rate of weight loss during an afternoon nap. The subject, T. H., weighed 11.68 Kg. The room temperature was 76.5 F., and the relative humidity was 26 per cent.

advantage of having greater magnitude. During sleep the fluctuations over the trunk are often so small as to be difficult to measure accurately. Charts 2 and 5 illustrate the type of change observed during sleep, namely, an initial rise and then a fall. The effect of environment on this rise and fall was studied, the index used being the rate of fall subsequent to any rises that occurred at the onset of sleep. The fall rather than the rise was used for the same reasons as in the case of evaporation.

In chart 6 the rate of fall has been plotted against room temperature for 67 experiments. Although a great deal of scatter is present, it is nevertheless apparent that cooling of the foot is relatively slight in a warm room. In warm rooms the greatest change in evaporation was

5. An exception to this statement is the skin over the shin, which for temporary periods may cool while the sole is warming or warm while the sole is cooling.

shown to occur. It seems that the cutaneous temperature even before sleep under such conditions is already at a maximum and can rise no more, so that without an initial peak there can be no fall. With more moderate room temperatures there is rapid cooling, which can take place only by virtue of a high initial rise. With still lower room temperatures the rate of fall again decreases. This decrease is to be expected because there is only a slight, or even no, initial rise, vasoconstriction apparently relaxing little at the onset of sleep. A running mean through these data is included in chart 6 for greater clarity.

Effect of Environment on Fall in Rectal Temperature.—In foregoing paragraphs the fall in rectal temperature and the mechanisms of heat loss which appear to control this fall were commented on. Is this control completely effective, or does the environment affect the fall in rectal

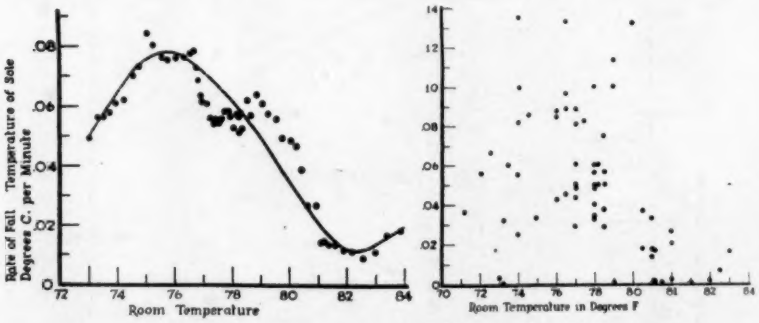

Chart 6.—The effect of environment on fluctuation in cutaneous temperature during sleep.

temperature? The table and chart 3 supply data relative to this point. Chart 3 shows that for the whole group of 96 experiments the fall is decreased by warm and humid environments. The value for chi square here was 4.3 (of borderline significance), tested by the method previously described.

The fact that environment exerts this demonstrable effect on the fall in rectal temperature cannot be taken to mean that regulatory mechanisms do not attempt to keep the fall constant. Certainly, one could not expect these mechanisms of control to be effective under all environmental stresses. A point must be reached on the scale of increasing temperature and humidity at which the body is totally unable to lose heat, and it is not unreasonable to think that in lower regions of the scale some effect of changing environment will remain even though the regulating mechanisms become increasingly effective. Furthermore, the table shows that the greater fall in rectal temperature in a cool, dry

environment than in a warm, humid environment resulted from a higher body temperature while awake and not from a lower body temperature during sleep.

COMMENT

Data have been presented which show that during sleep the body reacts as though the physiologic thermostat is set for a lower level of body temperature. This is a corollary to what appears to happen during muscular exercise, when body temperature is regulated about a higher level, as was shown by Nielsen.[6] The technics described also permit speculation as to the relative importance in temperature regulation of a central mechanism and of peripheral temperature sense receptors. Thus, at the onset of sleep it is hardly conceivable that there can be any change in the surroundings of the peripheral receptors which would indicate a need for increased loss of heat. The sweating and vasodilatation that do occur, therefore, are probably directed by a central regulator. Curiously, the amount of sweating is quantitatively related to the environment, even though the latter has not changed during the period of transition from waking to sleeping. Again, when radiant heat is directed at the subject, the first result is increased sweating, which must be the response of a peripheral reflex since rectal temperature continues to fall. The decrease in sweating at the moment of leveling of the rectal temperature suggests the inhibition of this peripheral reflex by central impulses which can have arisen in response only to changes at the "heat center" and not to changes at the periphery of the body. If this interpretation is correct, the experiment of artificially increasing sweating at that moment during a nap when the fall in body temperature is being combated provides a situation in which central and peripheral regulatory mechanisms are working in opposite directions.

SUMMARY AND CONCLUSIONS

Simultaneous and continuous measurements were made of the rectal temperature, the cutaneous temperature and the rate of weight loss of children in different environments during the course of 96 afternoon naps.

Rectal temperature always falls at first and then becomes level so abruptly that some regulatory mechanism must be in operation.

The cutaneous temperature and the rate of weight loss (evaporation) rise at first and then fall. Statistical analysis of the 96 experiments shows that the initial rise is greater the warmer and more humid the environment.

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6. Nielsen, M.: Die Regulation der Körpertemperatur bei Muskelarbeit, Skandinav. Arch. f. Physiol. **79**:193, 1938.

The basal rate of evaporation when the subject is in a static state is diminished by increases in environmental humidity, except when active sweating is taking place.

Inhibition of active sweating occurs for a short time coincident with the abrupt cessation in the fall of rectal temperature. In cool environments, in which insensible perspiration forms the major part of loss by evaporation, no decrease in the loss by evaporation occurs at this moment.

An interesting speculation to account for the phenomena observed is that the physiologic thermostat is set for a lower level of body temperature during sleep and that the fall in body temperature is not the result merely of passive relaxation.

PRIMOGENITURE AS AN ETIOLOGIC FACTOR IN PYLORIC STENOSIS

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A survey of the cases of 436 patients with pyloric stenosis admitted over a period of twenty-five years, 1914 to 1939, to the Hospital for Sick Children in Toronto shows that 50 per cent of the 405 affected infants whose order of birth was known were first-born children. Still,[1] in 1927, on the basis of a study of 400 cases of pyloric stenosis gave a comparable figure of 48.5 per cent for the incidence of the disease in first-born children, and Penrose[2] cited the figures of 49 and 58 per cent from two studies, one of 221 and the other of 222 cases. Since pyloric stenosis has a genetic basis (Cockayne,[3] Sheldon[4] and Ford, McCreary and Brown[5]), and occurs more commonly in males (in 81.8 per cent of the cases in Toronto[6]), it is important to weigh the evidence for the importance of the prenatal environmental factors associated with primogeniture in the production of the disease.

In previous studies of primogeniture as a factor in disease (Pearson,[6] Still[1] and Cockayne and Penrose[7]) no census data for the community on order of birth were available for comparison, and only

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5. Ford, N.; McCreary, J. F., and Brown, A.: Evidence of Monozygosity and Disturbance of Growth in Twins with Pyloric Stenosis, Am. J. Dis. Child. **61**:41 (Jan.) 1941.

6. Pearson, K.: First Study of the Statistics of Pulmonary Tuberculosis, London, Dulau & Co., 1907; On the Handicapping of the First-Born, ibid., 1914.

7. Cockayne, E. A., and Penrose, L. S.: The Genetics of Congenital Pyloric Stenosis, unpublished data.

approximate figures could be reached through statistical reasoning, which was at times open to criticism (Greenwood and Yule [8]). Since 1928 order of birth has been included in the vital statistics of Canada,[9] as well as in the records of the department of public health of Toronto; so this information was available for the present study.

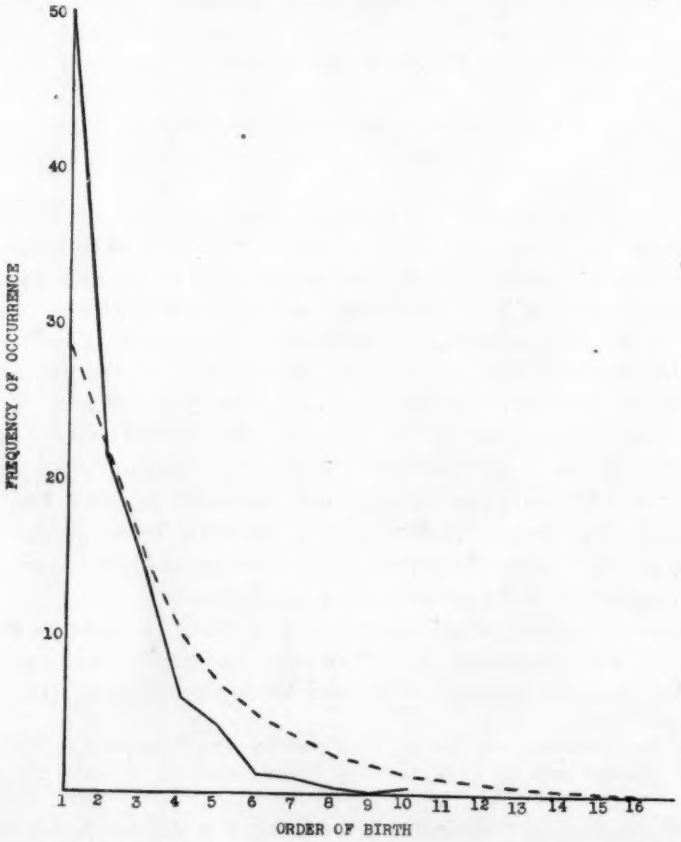

Chart 1.—Order of birth in 405 cases of pyloric stenosis (solid line), 1914 to 1939, and in 651,009 births in Ontario (broken line), 1928 to 1937.

Of the 436 cases of pyloric stenosis here reviewed, data regarding order of birth were available in 405, in 50.1 per cent of which the patient was a first-born child. This figure is markedly larger than that of 28.6 per cent, which represents the proportion of first-born children among the total number born in the province of Ontario during a ten year period (chart 1).

8. Greenwood, M., and Yule, G. U.: On the Determination of Size of Family and of the Distribution of Characters in Order of Birth from Samples Taken Through Members of the Sibships, J. Roy. Statist. Soc. **77**:179, 1914.

9. Vital Statistics, Ottawa, Canada, Dominion Bureau of Statistics, 1928-1937.

In this comparison a correction is desirable, however, before the excess of first-born children among the patients with pyloric stenosis is accepted as significant, since the majority of our patients (68.6 per cent) were born in the city of Toronto, where the average family is smaller and the percentage of first-born children is correspondingly higher than in the rural parts of the province. Order of birth of the patients born in the city should be compared not with that of the children born in the whole province but with that of children born in the city alone.

The information regarding order of birth of children born in Toronto is available only for the years 1928, 1933 and 1937,[10] while the cases of pyloric stenosis occurred over a period of twenty-five years, from 1914 to 1939. This disparity in data makes comparison difficult, since there is

Order of Birth of Patients with Pyloric Stenosis and of Infants Born in Toronto in 1928, 1933 and 1937

Order of Birth	Patients with Pyloric Stenosis Born in Toronto Admitted to the Hospital for Sick Children, 1914 to 1939		Average Number of Children Born per Year in Toronto in 1928, 1933 and 1937	
	Number	Percentage	Number	Percentage
First	144	51.8	4,748	41.2
Second	61	21.9	2,730	23.8
Third	41	14.7	1,627	14.1
Fourth	16	5.8	916	8.0
Fifth and over	16	5.8	1,476	12.9
Total	278	100.0	11,497	100.0

a definite change in the percentage of first-born children among the infants born in Toronto during the quarter of a century; this change is reflected in the figures for the ten years for which information is available. In 1939 the percentage of first-born children was 45.8 per cent; in 1933, 40.2 per cent, and in 1928, 38.6 per cent of the total births. In 1914 the percentage of first-born children must have been still lower. However, for comparison with the patients with pyloric stenosis an average percentage for the three years for which information is available has been used (41.2 per cent), although this figure is known to be too high.

The table and chart 2, which give the percentage distribution for order of birth, show that among patients with pyloric stenosis 51.8 per cent were first-born children, while the average percentage of first-born children among the total number of infants born in Toronto (during the three years) was 41.2 per cent. This difference of 10.6

10. These data were compiled for us by the department of public health of Toronto.

per cent is shown to be significant by the chi square test ($X^2 = 5.666$) and by Fisher's table (X^2 for n = 1 degree of freedom, P = 0.02). A difference as great as this, which would be produced by chance in less than 2 per cent of trials, is statistically significant.

There still remains the problem raised by Cockayne and Penrose [7] of whether limitation of the size of the family is practiced by parents

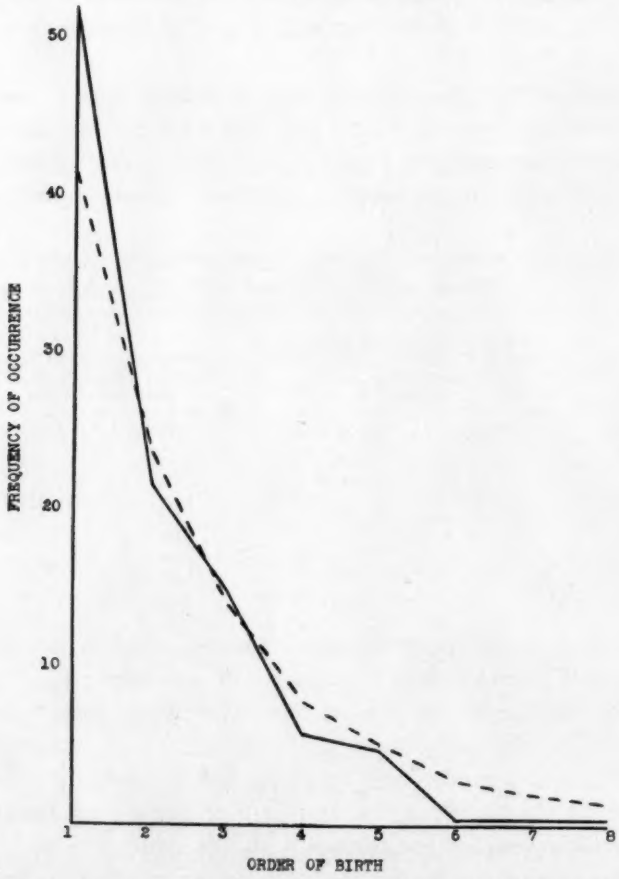

Chart 2.—Order of birth in 278 cases of pyloric stenosis in infants born in Toronto (solid line), 1914 to 1939, and in 34,493 births in Toronto (broken line) in 1928, 1933 and 1937.

who have had a child with pyloric stenosis. Cockayne and Penrose have shown that such limitation would increase the proportion of affected first-born children. However, one of us (A. B.), on the basis of his experience, is of the opinion that no such limitation is evident, since the parents of affected children accept the condition as one of the milder abnormalities which can be corrected by surgical intervention.

Indeed, the majority of the parents have little idea of the meaning of pyloric stenosis. In a later survey of the families and kindred of patients with pyloric stenosis, the question of limitation will be investigated further. For the present, the importance of primogeniture as an etiologic factor in pyloric stenosis is at least indicated.

SUMMARY

An investigation of the order of birth in 405 cases of pyloric stenosis showed that in 50.1 per cent the patient was a first-born child. Sixty-eight and six tenths per cent of the patients were born in Toronto, and of them 51.8 per cent were first-born children.

The census data on order of birth which were available both for the province of Ontario and for Toronto were used for comparison. Less than 41.2 per cent of the infants born in Toronto were first-born children, while 51.8 per cent of the patients with pyloric stenosis who were born in Toronto were first-born children. This difference of 10.6 per cent is shown to be statistically significant.

Although the question of whether there is voluntary limitation of family size by parents who have had an affected child remains to be answered, nevertheless the importance of primogeniture as an etiologic factor in pyloric stenosis is indicated.

JAUNDICE IN INFANTS AND IN CHILDREN

THE ICTERIC INDEX AS A METHOD OF DETERMINING THE TYPE OF JAUNDICE

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In a previous study [1] we obtained equal values for the icteric index of a series of specimens of cord blood and of blood from normal newborn infants by the water and by the acetone method. Since the values obtained by the two methods for several patients with congenital hemolytic icterus examined at that time were similar, we concluded that this test might be useful in differentiating the hemolytic type of jaundice from other types. Further studies were made, and 13 patients with hemolytic jaundice and 6 with nonhemolytic icterus caused either by intrinsic hepatic disease or by biliary obstruction were examined.

METHOD

The icteric index, a simple quantitative method for studying the degree of jaundice, was introduced by Meulengracht [2] in 1920. The serum is diluted directly with a physiologic solution of sodium chloride or water and matched with arbitrary standards of potassium dichromate solution. Hemolysis, which may be obscured, particularly in deeply jaundiced serum, introduces a serious error. In 1924 Ernst and Förster [3] modified this method. By adding acetone to the serum the proteins are precipitated, and if any hemolysis is present the hemoglobin is carried down with the proteins. The supernatant solution is then compared with the dichromate standards of Meulengracht. The acetone dilution is preferable to the water dilution because the supernatant solution is clearer. More reliable values can be obtained even for hemolyzed serum since the hemoglobin does not interfere.[4]

From the Pediatric Service of Dr. Béla Schick and the Laboratories of Mount Sinai Hospital.

1. Weiner, S. B., and Reiner, M.: Icteric Index in the Newborn, Proc. Soc. Exper. Biol. & Med. **41**:83, 1939.

2. Meulengracht, E.: Die klinische Bedeutung der Untersuchung auf Gallenfarbstoffe im Blutserum, Deutsches Arch. f. klin. Med. **132**:285, 1920.

3. Ernst, Z., and Förster, J.: Ueber die Bestimmung des Blut-Bilirubins, Klin. Wchnschr. **3**:2386, 1924.

4. The methods used in our laboratory are described in Reiner, M.: Manual of Clinical Chemistry, New York, Interscience Publishers, Inc., 1941.

In 1937 Newburger [5] compared the water and acetone methods by determining the icteric indexes of 222 specimens of serum. He found that the ratio between the icteric index of nonhemolyzed serum obtained by the water method and that obtained by the acetone method for the same specimen was about 2.5:1 or 3:1. The specimens were principally from patients with obstructive and hepatic jaundice, the so-called "regurgitative icterus," encountered in an active adult medical service.

The upper limit for the normal icteric index obtained by the water method is 10 units, and when the index is 15 units visible jaundice is present. The normal value obtained by the acetone method is 5 units, and jaundice can be seen with a reading of 8 units.

OBSERVATIONS

Hemolytic Type of Icterus.—We have examined specimens of serum for 13 patients with hemolytic icterus (table 1). Practically identical

TABLE 1.—*Icteric Index for Thirteen Patients with Hemolytic Type of Jaundice*

Case No.	Diagnosis	Icteric Index Units: By Water Method (W)	By Acetone Method (A)	Ratio * W/A
1	Congenital hemolytic icterus	12	12	1.00
2	Congenital hemolytic icterus	24	20	1.20
3	Congenital hemolytic icterus	20	18	1.11
4	Congenital hemolytic icterus	48	48	1.00
5†	Acute hemolytic anemia	20	14	1.43
6†	Erythroblastosis foetalis	35	27	1.29
7	Icterus gravis and anemia of the newborn	19	14	1.36
8	Hypertrophic pyloric stenosis and icterus neonatorum	17	15	1.13
9	Sickle cell anemia	42	36	1.17
10	Sickle cell anemia	45	45	1.00
		35	30	1.17
11	Sickle cell anemia	16	12	1.33
12	Sickle cell anemia	14	10	1.40
13	Sickle cell anemia	12	8	1.50

* The average W/A ratio was 1.22.

† There was a trace of hemolysis in the serum.

values for the icteric index were obtained by the water and by the acetone method. The ratio of the index obtained by the water method to that obtained by the acetone method (W/A) was about 1:1, although for a few slightly hemolyzed specimens the index obtained by the water method was somewhat increased, which resulted in a slightly higher ratio.

CASE 1.—*Congenital hemolytic icterus.*

The patient was an 8 month old Negro child who had low grade continuous icterus, moderately severe anemia, a palpable spleen, an increased reticulocyte count and slightly increased fragility of the erythrocytes. Several transfusions gave temporary relief.

5. Newburger, R. A.: Determination of Icteric Index by Acetone Method, J. Lab. & Clin. Med. **22**:1192, 1937.

CASE 2.—*Congenital hemolytic icterus.*

The patient was an 18 year old youth who had had pain in the right upper quadrant, anemia, jaundice, splenomegaly and increased fragility of the erythrocytes for many years.

CASE 3.—*Congenital hemolytic icterus.*

The patient was a 3½ year old girl who had had anemia almost since birth. Many transfusions were given. Anemia, icterus, microcytosis, splenomegaly and increased fragility of the erythrocytes were present.

CASE 4.—*Congenital hemolytic icterus.*

The patient was a boy of 12 years whose disease began at 8 years of age with severe anemia which followed an infection. A transfusion was required, and splenomegaly was observed. Typical microcytosis was present, and successive episodes of anemia and icterus, with slightly increased fragility of the erythrocytes, have occurred. The father of the child also has microcytosis.

CASE 5.—*Acute hemolytic icterus.*

The patient was an 8 month old child in whom icterus, severe anemia and elevated temperature suddenly developed but the blood smears remained normal. The child improved after transfusions. There has been no recurrence of the jaundice and anemia for three years.

CASE 6.—*Erythroblastosis foetalis.*

The patient was a newborn child who had jaundice, moderate anemia, hepatosplenomegaly and an increased number of circulating immature red cells. He recovered after repeated transfusions.

CASE 7.—*Icterus gravis and anemia of the newborn.*

The patient was a 4 week old infant born with marked jaundice, in whom moderate anemia developed. Jaundice gradually disappeared, and the anemia remained at a constant level. Hepatosplenomegaly was present. There were no circulating erythroblasts, but marked erythroblastic activity, particularly normoblastic, in the bone marrow was noted. The infant recovered after a transfusion.

CASE 8.—*Hypertrophic pyloric stenosis and icterus neonatorum.*

The patient was admitted to the hospital in the second week of life with hypertrophic pyloric stenosis and intense jaundice. The question of congenital biliary obstruction was raised, but the jaundice disappeared in one week. Results of an examination of the blood were normal.

CASE 9.—*Sickle cell anemia.*

The patient, a 12 year old Negro boy, had the signs and symptoms of sickle cell anemia and a history of having had the disease for six years. The specimen of blood examined was obtained during a remission.

CASE 10.—*Sickle cell anemia.*

The patient, a 4 year old Negro child who had the usual signs and symptoms of sickle cell anemia, had been admitted to the hospital many times for recurrent crises of severe icterus and anemia.

CASE 11.—*Sickle cell anemia.*

The patient was the 6 year old brother of the patient in case 9. The results of hematologic examinations were typical of sickle cell anemia. The patient had had many crises and attacks of pneumonia, and the first specimen examined was obtained while he was in the hospital with pneumonia.

CASE 12.—*Sickle cell anemia.*

The patient, an 8 year old Italian boy, had sickle cell anemia of three years' duration.[6] The specimen was taken while he was apparently free of symptoms.

CASE 13.—*Sickle cell anemia.*

The patient was the 4 year old brother of the patient in case 12. Anemia and icterus developed about two years after his brother's disease was diagnosed. The results of hematologic examinations were typical of sickle cell anemia.

Nonhemolytic or Regurgitative Type of Icterus.—We have examined specimens of serum from 6 patients with the nonhemolytic, or regurgitative, type of icterus. The ratio of the icteric index obtained by the water method to that obtained by the acetone method for these patients varied from 1.7 to 4.6, a range of values resembling that of Newburger.

TABLE 2.—*Icteric Index for Six Patients with Nonhemolytic (Regurgitative) Type of Jaundice*

Case No.	Diagnosis	Icteric Index Units: By Water Method (W)	By Acetone Method (A)	Ratio W/A
14	Catarrhal jaundice (infectious hepatitis)	26	15	1.73
15	Subacute yellow atrophy of the liver	300	90	3.33
16	Cirrhosis of the liver (with pulmonary tuberculosis)	19	11	1.73
		11	6	1.83
17	Cirrhosis of the liver	45	20	2.25
18	Congenital obstruction of the bile ducts	110	40	2.75
19	Biliary cirrhosis with intermittent biliary obstruction and congenital hemolytic icterus	135	39	3.46
		37	10	3.70
		32	7	4.57

CASE 14.—*Catarrhal jaundice.*

The patient was an 8 year old boy with mild icterus, some enlargement of the liver and spleen and fever of one week's duration.

CASE 15.—*Subacute yellow atrophy of the liver.*

The patient was a 10 year old girl who had icterus, abdominal distention, rapidly developing cholemia and enlargement of the liver. She died, and the observations at autopsy substantiated the clinical diagnosis.

CASE 16.—*Cirrhosis of the liver.*

The patient was an 11 year old girl who had hepatosplenomegaly of several months' duration and transient icterus. Active pulmonary tuberculosis developed. A punch biopsy of the liver was done, and the presence of a cirrhotic process in the liver was reported. She died.

CASE 17.—*Cirrhosis of the liver.*

The patient was a 7 year old child who had ascites, a large liver and moderate icterus. A clinical diagnosis of Laennec's type of cirrhosis was made. The child is still under observation.

6. Weiner, S. B.: Sickle Cell Anemia in an Italian Child: A Case Report, J. Mt. Sinai Hosp. **4**:88, 1937.

CASE 18.—*Congenital obstruction of the bile ducts.*

The patient was a 5 week old infant who had progressive icterus and clay-colored stools, with bile in the urine. An exploratory laparotomy revealed no anomaly in the extrahepatic biliary system. The gallbladder was collapsed. A probe was pushed through the common duct into the liver, and a drainage tube was left in situ. After this, bile appeared in the stool, and the jaundice slowly disappeared. Pyelonephritis also developed, caused probably by a congenital deformity in the genitourinary tract. The liver has remained enlarged.

CASE 19.—*Biliary cirrhosis, intermittent obstruction and congenital hemolytic icterus.*

The patient was a 6 month old child with a history of severe anemia at birth which required many transfusions. This was followed by two episodes of deep jaundice, with clay-colored stools and dark urine. (The first specimen of blood was obtained during such an attack.) The child's liver and spleen were enlarged. Examination of the blood showed increased fragility of the erythrocytes and anemia. After two days in the hospital the jaundice rapidly diminished, and bile suddenly reappeared in the stool. Subsequent specimens of blood obtained at this time and shortly before discharge showed latent icterus.

The 4 cases of congenital hemolytic icterus were typical examples of the disease. The ratio of the icteric index obtained by the water method to that obtained by the acetone method was nearly 1 : 1. In case 1, our laboratory report was of considerable help in determining the origin of the anemia and icterus. This child did not have typical microcytosis or greatly increased fragility of the red cells.

According to our results the cases of erythroblastosis and of icterus gravis fell into the hemolytic group. There is still, however, considerable discussion as to the exact nature and cause of the many clinical syndromes grouped together as "icterus gravis."[6a] Our results indicate the hemolytic origin of the anemia and icterus in these cases, since the ratio of results by the water method to those by the acetone method varies little from 1 : 1. One must make some allowance for the difficulty of obtaining samples of blood completely free of hemolysis from newborn infants. Although hepatic damage may be an important factor in causing the icterus of some of these infants, we should like to emphasize the hemolytic character of the icterus of these 2 infants.

In the case of the infant with icterus and pyloric stenosis, our results were of considerable clinical value on admission. The 1 : 1 ratio resembled that typical for normal newborn infants and pointed to a diagnosis of physiologic icterus rather than of biliary obstruction.

The 5 cases of sickle cell anemia are all typical examples of this disease. Hematologists generally agree that the anemia and icterus in cases of this type are due to a hemolytic process present in addition to the sicklemia. Our results favor this view. We must point out, however,

6a. Zuelzer, W. W., and Bigler, J. A.: Disturbances of Hepatic Function in Icterus Gravis, Am. J. Dis. Child. **60**:873 (Oct.) 1940.

that in spite of taking every possible precaution to avoid hemolysis when obtaining blood samples in these cases, only 1 specimen showed a perfect 1 : 1 ratio. In 3 cases the ratios ranged from 1.24 to 1.50. It is easily conceivable that the long-continued anemia and hemolytic process in these children had led to changes in the liver parenchyma and that some "regurgitative" jaundice was also present.

Cases 14, 15, 16 and 17 are examples of primary hepatic disease, in which there are varying degrees of parenchymal injury and destruction. In all these cases the ratio of the icteric index obtained by the water method to that obtained by the acetone method is high.

Case 18 is probably an example of intrahepatic biliary obstruction, which was partially relieved by operation.[6b]

Case 19 is an excellent example of hemolytic icterus resulting in, or associated with, biliary disease, cirrhosis of the liver and intermittent biliary obstruction. The damage to the parenchyma of the liver and the biliary obstruction result in the regurgitative type of icterus. The ratio of the icteric index obtained by the water method to that obtained by the acetone method should therefore be high. If the child recovers completely from her hepatic injury, one would expect to find the ratio close to 1 : 1, as in cases of uncomplicated congenital hemolytic icterus.

COMMENT

The relation of the icteric indexes determined by the water and acetone methods may be explained by a difference in the physical state of the bilirubin in cases of regurgitative and of hemolytic icterus. The currently accepted concept of bile physiology is that bilirubin is formed in the elements of the reticuloendothelial system throughout the body. It is then secreted by the liver cells into the bile ducts. In cases of hemolytic icterus an excessive amount of bilirubin is formed, and its delayed secretion through the liver leads to jaundice. In cases of the obstructive, or regurgitative, type of jaundice, bilirubin has passed from the reticuloendothelial system through the liver cells into the biliary tract. An obstruction in the bile passages or injury to the hepatic cells results in the reabsorption of the bilirubin into the blood stream and leads to jaundice.

Value of the Ratio of the Icteric Index Obtained by the Water Method to That Obtained by the Acetone Method.—This ratio offers a simple means of identifying hemolytic jaundice and of differentiating it

6b. Since submitting this manuscript, we have had the opportunity to examine the serum of another infant for whom an operative diagnosis of congenital absence of the bile ducts was made. The icteric index was 83 units by the water method and 17 units by the acetone method, with a ratio between the two values of 4.88.

from the nonhemolytic types. Since hemolysis will increase the icteric index obtained by the water method, the following precautions must be observed to obviate error:

1. An absolutely clean, dry syringe and dry needle must be used.
2. The alcohol or other antiseptic used on the skin must be allowed to dry completely.
3. The blood must be drawn and transferred slowly into a clean, dry tube. It must not be "squirted."
4. The specimen must be allowed to clot thoroughly and to loosen from the tube. The serum should be separated from the clot by centrifuging after half an hour.

In cases in which both hemolytic and nonhemolytic icterus are present, as in case 19, the ratio will be high—the reaction of regurgitative icterus. Other clinical and hematologic evidences of hemolytic icterus must be looked for in these cases.

Type of Jaundice in Cases of Icterus Neonatorum.—The theory of a hemolytic origin of the icterus is the most acceptable explanation for the pathogenesis of icterus neonatorum. There is no evidence that either biliary obstruction or hepatitis is the cause of physiologic icterus in the newborn. On the other hand, many investigators have correlated the neonatal fall of hemoglobin and red blood cells with the clinical appearance of jaundice and the rise of the icteric index in the period immediately after birth.[7] They have presented this as evidence of the existence of the hemolytic type of icterus. We feel that our observations are further evidence in support of the theory of a hemolytic origin of icterus neonatorum.

SUMMARY

The determination of the icteric index of a specimen of jaundiced serum by both the water and the acetone method is proposed as a means of differentiating the hemolytic from the nonhemolytic type of jaundice.

In cases of pure hemolytic icterus the ratio of the icteric index obtained by the water method to that obtained by the acetone method is 1 : 1.

Icterus neonatorum falls into the group of hemolytic icterus according to this test.

Dr. Herman Schwarz gave permission to use data for 3 patients with icterus admitted to the pediatric service of Beth Israel Hospital, New York. Dr. Harry Sobotka gave support and advice in this work.

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7. Goldbloom, A., and Gottlieb, R.: Icterus Neonatorum, Am. J. Dis. Child. **38**:57 (July) 1929. Bonar, B. E.: The Icterus Index in the Newborn Infant, ibid. **50**:1143 (Nov.) 1935.

Case Reports

HAND-SCHÜLLER-CHRISTIAN DISEASE

A CASE IN WHICH LYMPHADENOPATHY WAS A PREDOMINANT FEATURE

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ELIZABETH, N. J.

Reports of cases of Hand-Schüller-Christian disease are so numerous and the clinical symptoms characteristic of the malady so well known that the addition of another case to the literature seems justified only because it presented unusual clinical and pathologic features.

REPORT OF CASE

H. G., the first child of 25 year old Scotch-Irish parents, was delivered normally at full term. For the first three months, he was breast fed, after which he was given a mixture of cow's milk with dextrin and maltose. His succeeding diet was the one usual for his age. He received the standard amounts of orange juice and cod liver oil, and his appetite remained good until his entrance to Mount Sinai Hospital, at the age of 9 months. His growth and development were normal, and there was no history of illness. He sat up at 5 months, stood up in his crib at 8 months and had eight teeth at 9 months of age. No immunizations had been given. He used a few words, and his general reactions were those of a normal child. His parents were in good health; there was no allergy or disease of the blood. The maternal grandmother had died of tuberculosis many years before.

In February 1937, at the age of 7 weeks, a lump was noted in the infant's left groin, and this slowly increased in size. There was no associated pain or tenderness. At 4½ months of age a growth was noted behind the right ear. As this increased in size a similar lump appeared high on the left side of the neck. He continued to progress normally in weight, ate well and was bright and active.

On September 17, at the age of 7 months, he was first seen by one of us (M. L. R). His weight of 22 pounds 14 ounces (10.4 Kg.) and length of 28 inches (71 cm.) were above the average for his age. There was moderate pallor, but otherwise, except for the specific conditions which are to be mentioned, he was physically normal. He had marked enlargement of the upper part of the neck, which included the areas of the cervical and the postauricular nodes on both sides and gave him a bull-necked appearance (fig. 1). There were an enlarged gland in the left inguinal area, about one-half the size of a walnut, and moderate enlargement of the right inguinal nodes. These glands felt firm and discrete and were not adherent to the skin. The mother expressed the belief

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that the mass decreased slightly at times. There was no pain or tenderness. Three days later he was sent to the Elizabeth General Hospital with the suggested diagnosis of Hodgkin's disease, cystic hygroma of the neck or tuberculous lymphadenitis. The following data were obtained during his stay of ten days in the hospital: There were 3,900,000 red blood cells and 12,000 white blood cells per cubic millimeter, with 84 per cent polymorphonuclears, 14 per cent lymphocytes, 1 per cent mononuclears and 1 per cent eosinophils. The hemoglobin content was 65 per cent. The reactions to the Kahn and Wassermann tests were negative. The bleeding time was two and a half minutes; the clotting time, four and a half minutes. Examination of the urine gave negative results. The report of a roent-

Fig. 1.—The patient at the age of 9 months.

gen examination read: "The widening of the mediastinal shadow resembles that from an enlarged thymus gland. The long bones show no definite pathologic changes."

Preceding the excision of the left inguinal node, the infant's temperature was normal. The gland was mushy and friable. It appeared well demarcated, but the under surface was firmly attached and could not be freed easily. It was removed in fragments. A pathologic report of the biopsy follows.

The material consisted of small pieces of gray, friable tissue. Microscopically, the lymphoid structure was entirely replaced by diffuse proliferation of epithelioid cells and giant cells, some of which were of the classic Langhans type but others of the foreign body type. Intermixed with this basal structure was diffuse infiltration with pyknotic polymorphonuclears and eosinophils. Here and there

were clusters of lymphocytes and occasional small areas of necrosis. There was nowhere any histologic evidence of Sternberg's disease. The diagnosis was chronic hyperplastic, tuberculous lymphadenitis.

After discharge, the infant was given ultraviolet therapy. In all, he received eleven treatments between October 2 and November 5, the time of exposure being gradually increased from one and a half to five minutes. He was given general radiations to the body and local applications to the glands.

Roentgenograms of the lungs of both parents taken during this period showed nothing abnormal. The child's film showed only "exaggerated root shadows and bronchial markings." The mother had a positive reaction to the Vollmer tuberculin patch test.

As the child's reaction to the tuberculin test with 0.2 mg. and later with 1 mg. of purified protein derivative was negative and there was no response whatever to the treatments with ultraviolet light, he was admitted to Dr. Béla Schick's service, Mount Sinai Hospital, on November 10. Five days prior to admission, the baby had a chill, followed by a temperature of 105 F. and accompanied by profuse perspiration and a respiratory rate of 40. Physical examination, however, revealed no definite disease, and when the illness subsided after three days it was called "grip." This attack was followed by dry cough and increased pallor. During this episode the patient appeared sicker than would be expected from the physical findings and the short course of the illness.

First Admission to the Hospital.—Results of physical examination on admission were the same as previously noted except that the spleen was palpable 2 to 3 cm. below, and the liver 3 cm. below, the costal margin. The mucous membranes were pale. There was no respiratory difficulty. A smear of the bone marrow showed no abnormalities. Reactions to the Wassermann and the Kahn test were negative. The laboratory reported a hemoglobin content of 42 per cent. There were 3,062,000 red blood cells and 11,700 white blood cells per cubic millimeter, with 300,000 platelets. There were 77.5 per cent neutrophils, 12 per cent lymphocytes, 4.5 per cent mononuclears and 5.5 per cent juvenile forms. The sugar in the blood measured 68 mg., the cholesterol 195 mg. and the cholesterol ester 138 mg. per hundred cubic centimeters. Other determinations on the blood, including those of proteins, calcium and carbon dioxide–combining power, were within normal limits. A roentgenogram of the lungs showed "nodular enlargement of the superior portion of the mediastinum, suggesting mediastinal glands." Roentgen examination of the long bones and the skull gave normal results (fig. 2 *A*).

The report of the biopsy performed November 20 on three lymph nodes excised from the posterior triangle of the right side of the neck was as follows: There was granuloma of the lymph nodes, characterized by excessive proliferation of reticular cells, with the formation of syncytial reticulum giant cells. There was focal necrosis of the granuloma; the infiltration with isotropic and a little anisotropic fat was probably secondary to necrosis. The histologic features were not characteristic of Hodgkin's disease or fully compatible with a diagnosis of lipoid granulomatosis (Hand-Schüller-Christian disease).

These sections showed essentially the same changes as those taken from the inguinal node previously removed, on which the diagnosis of tuberculosis was made. It is interesting that Hand, who first described the disease, also thought he was dealing with atypical tuberculosis. Culture of tissue from the gland failed to yield tubercle bacilli.

On admission, the infant weighed 24 pounds 15 ounces (11.3 Kg.), and on November 30, 21 pounds 3 ounces (9.6 Kg.). Afebrile diarrhea had developed

on November 21, which lasted seven days. He had poor appetite and exhibited malaise at the onset, but his general condition improved rather rapidly. Despite the uncertainty of the diagnosis, high voltage roentgen therapy was started on November 30. Within ten days 400 r, as measured in air with high voltage was administered through fields measuring 10 by 10 cm. to the right and left sides of the neck. As the white blood cell count reached 2,500, roentgen therapy was stopped. He became pale, dry and listless and refused most of his food. The turgor of the skin was poor. The weight on December 15 was 18 pounds 8 ounces (8.4 Kg.). Three transfusions were given, the amounts varying from 150 to 200 cc. of citrated blood. Five per cent dextrose in physiologic solution of sodium chloride was administered intravenously on several occasions. The cervical glands shrank considerably during the period of roentgen therapy and the roentgenogram showed "marked diminution in the bilateral masses seen in the superior portion of the mediastinum." On December 1 determinations on the

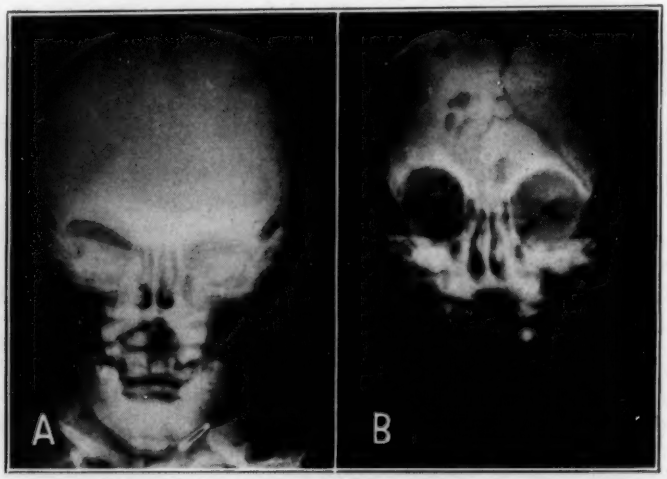

Fig. 2.—Roentgenograms of the skull: *A*, at 9 months of age; *B*, at 14 months.

blood showed: cholesterol 185 mg. per hundred cubic centimeters, esterified cholesterol 135 mg., sugar 68 mg., urea nitrogen 11 mg., calcium 9.4 mg., albumin 3.5 Gm., globulin 2.3 Gm. and carbon dioxide-combining power 51.4 volumes per cent. Diarrheal stools showing Bacillus coli on culture recurred. Moderate cyanosis over the body, with some accentuation about the umbilical area, was noted. There were no palpable abdominal masses. The spleen and liver were the same size as on previous examination. An abdominal roentgenogram was normal. The child was apathetic. The prognosis seemed poor. On January 1 his weight reached its lowest point, 16 pounds 14 ounces (7.7 Kg.). All of the lymph nodes were much smaller. Blood transfusion was given on this day and again on January 26, 200 cc. being given each time. Between these dates there occurred slow but steady improvement, until on January 26 his weight had reached 19 pounds 2 ounces (8.7 Kg.). The white blood cell count was 9,000 per cubic millimeter and the hemoglobin content, 83 per cent. Although the glands had enlarged slightly, the child was more active and alert. On February 1 he was discharged from the hospital, weigh-

ing 19 pounds 6 ounces (8.8 Kg.), with the tentative diagnosis of reticulum cell sarcoma of the lymph nodes.

Subsequent Course.—Three weeks after discharge his weight had increased by 4 pounds (1.8 Kg.), and his general condition was good. The lymph nodes were only slightly enlarged.

The child was seen again in the latter part of March; the mother had noticed two nodules over the occiput about the size of large almonds. He was readmitted to Mount Sinai Hospital. A roentgenogram of the skull showed thickening of the frontal bone, of both the inner and the outer table. Numerous areas of rarefaction, irregular in outline and size, were scattered throughout the skull but largely in the outer table and the medullary cavity (fig. 2*B*). Biopsy of one of the nodules of the scalp showed the same picture as that of the lymph glands.

When next seen, at the age of 19 months, in mid-September, the child had all his first teeth and was beginning to walk. However, all the glands had again become tremendously enlarged and masses were felt on rectal examination. The liver and the spleen were the same size as before. A roentgenogram of the skull showed defects more extensive than those observed in March, and there were new areas of rarefaction in the upper end of the right tibia, the upper end of the left humerus and the lower part of the right humerus.

On November 11 the cervical nodes were still enlarged. One on the left side was about the size of a plum. Both axillary regions had areas of induration, and both thighs exhibited diffuse enlargement. The superficial veins of the middle of the abdomen were conspicuous.

On Jan. 4, 1939, at the age of 23 months, he weighed 32 pounds 10 ounces (14.8 Kg.). The swellings on the thighs had decreased slightly. The one on the right was the size of a lemon, while the one on the left was slightly smaller. Both thighs felt soft except for several bean-sized nodes within them.

In the interval between March 13, 1938 and Jan. 28, 1939 the child received the following roentgen therapy: from March 16 to May 14, 1938, 150 r, as measured in air, to five overlapping fields over the skull (Kienböck technic), with 125 kilovolts through a copper filter 0.25 mm. thick at a focal skin distance of 30 cm.; from November 19 to December 8, with 200 kilovolts through a copper filter 1 mm. thick at a focal skin distance of 50 cm., 200 r (measured in air) to a 10 by 10 cm. field over the left groin, 300 r to a 10 by 15 cm. field over the right groin and 100 r to a 10 by 10 cm. field in the left axilla; from Jan. 17 to Jan. 28, 1939, an additional 200 r was delivered to the skull, using the original factors.

On February 1 symptoms of a mild respiratory disorder developed. Two days later, when the condition appeared definitely worse, one of us (M. L. R.) was called in. The child was pale, had a respiratory rate of 40, coughed frequently and was perspiring profusely. Although he had vomited a few times and the mother believed that he had some abdominal pain, no definite intra-abdominal condition was suspected. His acute condition did not appear serious.

Two days later, his condition had become alarming and he was sent to the Elizabeth General Hospital. His breathing was rapid and shallow, his heart rate rapid and his pulse barely perceptible. His lungs exhibited only occasional rales and no areas of consolidation. The abdomen was distended and tympanitic, with prominent veins and some retraction of the umbilicus. He showed no response to treatment with cardiac stimulants, sulfanilamide and oxygen. He died the following noon, February 6.

Autopsy.—Autopsy was performed by Dr. Casilli, of the Elizabeth General Hospital. The body was that of a well developed, well nourished, pale child presenting enlargement of the lymph nodes on both sides of the neck, more marked on the right. Additional large nodes were found in the inguinal, axillary, peribronchial, anterior mediastinal and retroperitoneal areas. The mesenteric nodes were normal in size. They were all discrete, with thin capsules; on section they showed a homogeneous opaque structure, with irregularly placed yellowish areas. Similar yellowish areas were found in the kidneys. There were marked anemia and hyperplasia of the bone marrow. The spleen was moderately enlarged, but its gross structure was normal. The lungs showed discrete areas of bronchial

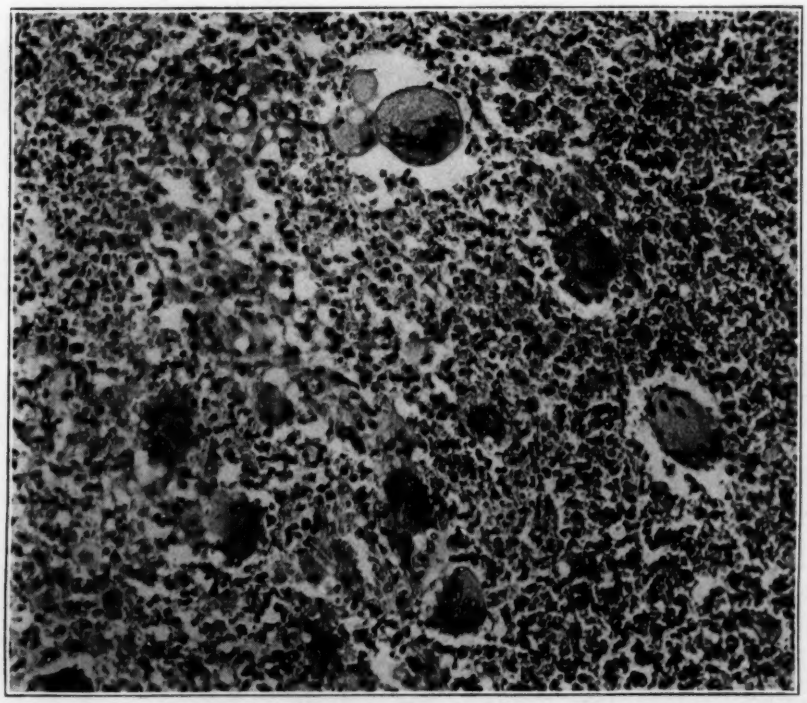

Fig. 3.—Section of a lymph node taken for biopsy, showing proliferation of reticulum cells and giant cells, intermingled with polymorphonuclear leukocytes, lymphocytes and plasma cells.

pneumonia. There was a diffuse purulent peritonitis, the result of an acutely inflamed ruptured appendix.

Second Study of the Lymph Node Removed for Biopsy.—A second microscopic study at Mount Sinai Hospital of the first lymph node removed for biopsy yielded the following description (Dr. P. Klemperer). The capsule showed slight infiltration with lymphocytes. The normal architecture was obliterated and in great part replaced by a diffuse proliferation of large polygonal cells, with large oval, occasionally indented, pale nuclei, distinct nucleolar membranes and generally one or two nucleoli. The abundant cytoplasm was often vacuolated. Often these

cells were large, and many multinucleated giant cells were intermingled with them (fig. 3). The nuclei of these giant cells were identical with those of the mononuclear cells, and the cytoplasm showed distinct vacuoles. These cells, which were proliferated histiocytes, had replaced large areas of lymphatic tissue. Intermingled with them were plasma cells, lymphocytes and polymorphonuclear leukocytes, many of which were eosinophils. Necrosis was observed frequently in the center of the islands of this newly formed large-celled granulation tissue (fig. 4). The histiocytes and multinucleated giant cells on staining with sudan III showed many large and small droplets, which often filled the entire cytoplasm. These fat droplets were not doubly refractile to polarized light. Only within the necrotic foci could small, doubly refractile particles be observed. In sections stained for

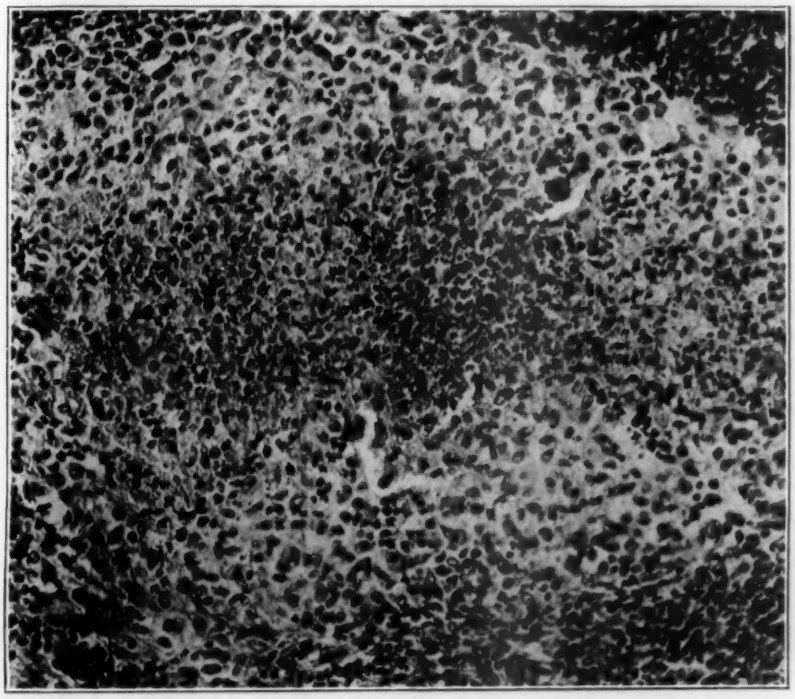

Fig. 4.—Section of a lymph node taken for biopsy, showing a large area of proliferation of histiocytes and reticulum cells, with central necrosis.

lipoids, after the method of Smith and Dietrich, some of the histiocytes contained small bluish black droplets, indicating a small amount of phosphatides. Mallory's trichrome stain did not reveal a conspicuous increase of the fibrillar reticulum.

This second biopsy of the axillary lymph node and the examination of a nodule from the skull showed identical pictures.

Microscopic Examination of Autopsy Material.—The autopsy material made available by Dr. Casilli, of the Elizabeth General Hospital, was examined microscopically by Dr. P. Klemperer of Mount Sinai Hospital.

Lung: Within the subpleural zones, extending for a considerable distance into the parenchyma were scattered small and large irregularly outlined nodules. They

consisted of large polygonal cells, with large pale nuclei and abundant cytoplasm, intermingled with lymphocytes, plasma cells and sporadic eosinophilic polymorphonuclear leukocytes and occasional nests of foam cells. There were numerous fibroblasts. The septums of the parenchyma frequently showed the same granulomatous infiltration. Small foci of bronchopneumonia were present.

Spleen: No significant changes were evident.

Liver: There was occasional infiltration of the periportal fields with large polygonal cells, with pale oval nuclei and abundant cytoplasm, intermingled with sporadic multinucleated giant cells, with identical nuclear structure, and lymphocytes, plasma cells and polymophonuclear leukocytes.

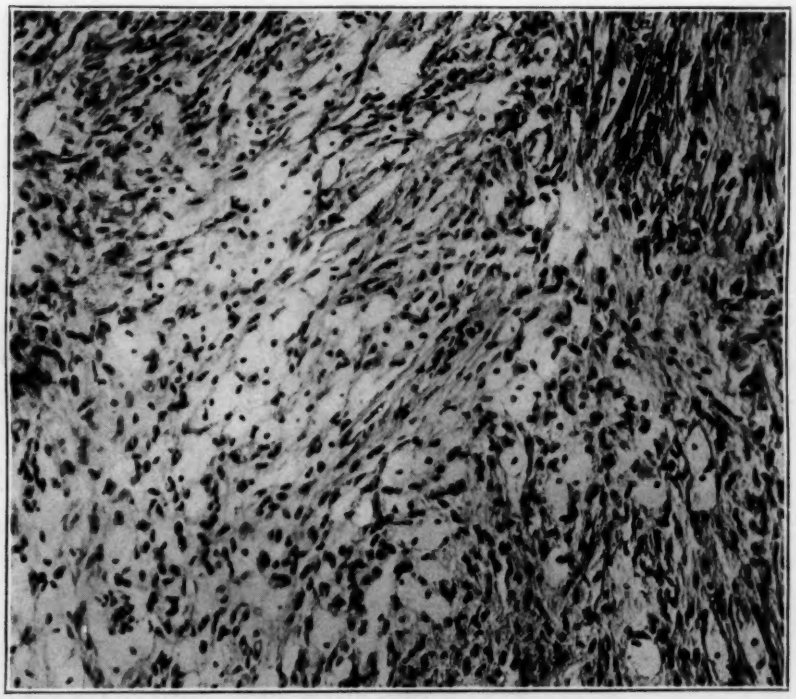

Fig. 5.—Paravertebral fascia, showing chiefly proliferation of fibroblasts and nests of foam cells.

Kidney: The cortex showed a few foci near the surface, of the same constitution as those in the liver and the lung.

Lymph Node: The picture was identical with that found in the specimens taken for biopsy.

Vertebrae: Sections from the vertebrae showed a dense tissue on the periosteum composed of fibroblasts intermingled with many large foam cells (fig. 5) and here and there nests of large polygonal cells, with pale nuclei and abundant cytoplasm, identical with those described in the lymph nodes and other organs.

Summary.—Progressive lymphadenopathy in a male infant started with enlargement of the inguinal lymph nodes at the early age of 7 weeks. At the age of 5 months cervical, axillary and mediastinal nodes were strikingly involved. Roentgen

examination of the skeleton at the age of 7 months did not reveal any defects, but reexamination four months later disclosed multiple defects in the membranous bones of the skull characteristic of Hand-Schüller-Christian disease. Exophthalmos and diabetes insipidus were absent throughout the course of the disease. With roentgen therapy, the general state of health of the child was well sustained and he developed normally. But in spite of persistent roentgen treatment, the lymphadenopathy and the skeletal lesions were never successfully controlled and reappeared when treatment was discontinued. The infant was in relatively good condition when he succumbed to generalized peritonitis from rupture of a gangrenous appendix. Biopsy of a lymph node performed at the age of 5 months disclosed replacement of the lymphoid tissue by diffuse proliferation of histiocytes and huge syncytial giant cells, mingled with lymphocytes, plasma cells and a conspicuous number of eosinophilic leukocytes.

At necropsy were found generalized lymphadenopathy and paravertebral and pulmonary infiltration with fibroblasts, histiocytes and large islands of foam cells, containing anisotropic fat droplets. The enlarged lymph nodes presented features similar to those observed previously. Limitations imposed on the autopsy prevented examination of the skeleton.

The enlargement of the lymph nodes, with moderate hepatosplenomegaly and associated anemia, and the normal white cell count suggested the diagnosis of Hodgkin's disease. However, the results of histologic examination of an excised lymph node did not confirm the diagnosis, because the syncytial giant cells were entirely different from the Sternberg type of giant cell. Their superficial similarity to Langhans giant cells suggested atypical tuberculosis, but the clinical picture and the absence of tubercles, caseation and acid-fast bacilli ruled out such a diagnosis. Letterer-Siwe disease was thought of, but the diagnosis could not be accepted because of the presence of fat within the reticulum cells and the syncytial giant cells. The appearance of defects in the membranous bones in the later phases of the disease led us to think of Hand-Schüller-Christian disease. The absence of exophthalmos and diabetes insipidus did not invalidate the diagnosis, for it is recognized that these symptoms are solely dependent on the incidental localization of granulomatous lesions at the base of the skull and therefore are not to be regarded as an essential feature of the disease process. The initial lymphadenopathy was certainly unusual, because enlargement of the lymph nodes, while it has been reported in Hand-Schüller-Christian disease, is generally only moderate. The histologic appearance of these lymph nodes was not typical either, because of the diffuse proliferation of the reticulum cells and the conspicuous syncytial giant cells, which differed from the foreign body giant cells commonly found in Hand-Schüller-Christian disease. Moreover, they, as well as the reticulum cells, contained only a small amount of neutral fat and no cholesterol. While the skeletal lesions found in the infant suggested Hand-Schüller-Christian disease, the diagnosis could not be definitely established because the clinical and pathologic features did not fully conform with it. The granulomatous infiltration of the paravertebral fascia and the lungs, with the enormous deposits of cholesterol within lipophages, observed at autopsy left no doubt that the tentative diagnosis made during life was correct.

COMMENT

Several features of the case seem to us deserving of emphasis. Hand-Schüller-Christian disease, while most frequent in infants and young children, rarely occurs at so early an age. The presence of moderately

enlarged lymph nodes has been noted in cases of Hand-Schüller-Christian disease. The case here reported is unusual because of the occurrence of such striking enlargement of the lymph nodes as the first, and chief, symptom followed only later by the characteristic skeletal changes. Only Flori and Parenti [1] have reported a case in which a similar dominating lymphadenopathy was observed, and the histologic changes in the lymph node they removed for biopsy were identical with those in our case. At autopsy, however, the lymph nodes, as well as the thymus, the parathyroid glands and the bones in their case, showed the classic lipoid granulomas of Hand-Schüller-Christian disease. In our case at autopsy the characteristic granulation tissue with foam cells was found to have infiltrated the paravertebral fascia and both lungs, while the lymph nodes exhibited only those changes which had been observed at biopsy. Our case and that of Flori and Parenti are of interest as presenting variants of the usual clinical picture of Hand-Schüller-Christian disease. Moreover, the histologic investigation during life and the autopsy afforded an opportunity to study the evolution of the morbid process.

Since Rowland's report [2] in 1928, this condition has been regarded by the majority of clinicians as an expression of a disturbance of cholesterol metabolism. On the contrary, pathologists, especially Letterer, have expressed the belief that the granulomatous lesion observed at biopsy and necropsy is specifically inflammatory and that "the cholesterol infiltration is by no means the cause of the granuloma formation but merely represents a characteristic associated feature of the granulomatosis." Letterer [3] called attention to the fact that a proliferation of reticulocytes and histiocytes initiates the granulomatous process and that only much later does deposition of lipoid occur within the established granuloma. In the case here reported, some areas of the lymph node showed a striking proliferation of reticulum cells with giant cells, while others showed the same cells intermingled with lymphocytes, plasma cells and polymorphonuclear neutrophilic and eosinophilic leukocytes—actual granulation tissue. Lipoid deposits were absent, although infiltration of giant cells with neutral fat was found. The typical lipoid granuloma was observed only at necropsy. This observation is in full support of Letterer's belief that the cholesterol is secondarily deposited within the granuloma and is not responsible for its formation.

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1. Flori, A. G., and Parenti, G. C.: Reticuloendoteliosi iperplasica infettiva ad evoluzione granulo-xantomatosa (tipo Hand-Schüller-Christian), Riv. di clin. pediat. **35**:193 (March) 1937.

2. Rowland, R. S.: Xanthomatosis and Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928.

3. Letterer, E.: Allgemeine Pathologie und pathologische Anatomie der Lipoidosen, Verhandl. d. Gesellsch. f. Verdauungskr. (1938) **14**:12, 1939.

SUMMARY

A case of Hand-Schüller-Christian disease is presented in which conspicuous lymphadenopathy as the first, and chief, symptom appeared at the early age of 7 weeks. Typical osseous changes appeared at the age of 13 months. While biopsy of the lymph nodes revealed histiocytic granulation tissue without cholesterol, at autopsy typical lipoid granulomas were observed.

MYASTHENIA GRAVIS

REPORT OF A CASE IN WHICH PROSTIGMINE METHYLSULFATE WAS USED

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AND

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Myasthenia gravis is an uncommon condition in childhood. The disease was first described by Willis [1] in 1672 and was recognized by Erb [2] as a clinical entity in 1878. The first case of the disease in childhood, described by Remak,[3] was that of a 12 year old girl. The relative infrequency of the condition in patients under the age of 17 years is illustrated by statistics from the literature. Palmer,[4] in reviewing the literature in 1908, found 8 such cases in a total of 126. Gerstle [5] cited 2 cases of the condition in patients under 10 years of age and 12 cases in persons under 20 years of age among 67 cases observed at the National Hospital in London between 1900 and 1927, but apparently these cases have not been reported. Kennedy and Moersch [6] noted that the onset of symptoms occurred in the second decade of the patient's life, in 7 of 87 cases studied at the Mayo Clinic. We have been able to collect from the literature altogether 34 cases in which the patient was under the age of 17 years. The average age of the patient in these cases was 11.8 years, and only 8 patients were under 10 years of age. The incidence was approximately equal in the two sexes. Two instances of

From the Department of Pediatrics, Morrisania City Hospital; Dr. L. H. Barenberg, Director.

1. Willis, T.: De anima brutorum, London, R. Davis, 1672, p. 288.

2. Erb, W.: Zur Casuistik der bulbären Lähmungen: III. Ueber einem neuen wahrscheinlich bulbären Symptomencomplex, Arch. f. Psychiat. **9**:336, 1878.

3. Remak, E.: Zur Pathologie der Bulbärparalyse, Arch. f. Psychiat. **23**:919, 1892; cited by Campbell, H., and Bramwell, E.: Myasthenia Gravis, Brain **23**: 277, 1900.

4. Palmer, A. S. M.: Myasthenia Gravis, Guy's Hosp. Rep. **62**:55, 1908.

5. Gerstle, M.: Myasthenia Gravis: Remarks on the Age Incidence; Report of a Case, California & West. Med. **30**:113, 1929.

6. Kennedy, F. S., and Moersch, F. P.: Myasthenia Gravis: A Clinical Review of Eighty-Seven Cases Observed Between 1915 and the Early Part of 1932, Canad. M. A. J. **37**:216, 1937.

the disease in siblings have been reported.[7] Because of the infrequency of the condition in childhood and the effective response by our patient to the administration of prostigmine methylsulfate, we considered it of interest to report a case which came under our observation.

REPORT OF CASE

A 9 year old girl was admitted to the Morrisania City Hospital on Dec. 21, 1938 in a state of collapse; she was unable to swallow and experienced difficulty in respiration. The family history was irrelevant, and the patient's past history was noncontributory. The illness which brought her to this hospital began about August 1937. There was an insidious onset of weakness, which was progressive. In April 1938 her voice acquired a nasal quality. Two months later she began to complain of difficulty in swallowing, especially of solid foods, and she had headache, dizziness and diplopia on occasions. She tired after walking two or three blocks and became unable to climb stairs.

On July 9, 1938 she entered another hospital, where bilateral ptosis and facial weakness on the right, as well as general muscular weakness, were found. The patellar reflexes on the right side were inconstant and sometimes absent. The laboratory data were not significant.

Between this time and the date of her admission to the Morrisania Hospital, the child was under the care of a private physician. All the symptoms previously mentioned persisted, and weakness progressed until she became bedridden and helpless. In November 1938, prostigmine bromide therapy was instituted. The immediate results were gratifying. The difficulty in speech, mastication and deglutition disappeared, and she was able to walk again. After a few weeks, however, fleeting episodes of difficulty in respiration began to occur and became progressively more frequent. On the evening of admission to this hospital, she had had an attack during which she became cyanotic and had a sense of suffocation.

On admission, the child was in a state of collapse, with rapid, shallow, labored respirations and marked cyanosis. She was conscious, well oriented and apprehensive. Oxygen was administered by nasal catheter, and 0.25 mg. of prostigmine methylsulfate was given subcutaneously, at once. About fifteen minutes later she appeared markedly improved and was comfortable and breathing calmly.

Physical Examination.—Physical examination at this time revealed a well developed and well nourished child, with a bright, intelligent expression. There was no ptosis of the eyelids; the pupils were round and equal and reacted to light and in accommodation. There was no nystagmus or palsy of the external rectus muscles. The ear drums and hearing were normal. The pharynx was not injected. There was no deviation of the uvula; the soft palate moved freely, and the tongue projected in the midline. There was no facial palsy. The heart lungs and abdomen were normal. The superficial reflexes were equal and active on the two sides. The deep reflexes were present but easily exhaustible. The Brudzinski, Kernig and Babinski signs were absent. There was no muscular atrophy or fibrillary tremors. Sensory examination revealed no abnormalities, and coordination was normal.

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7. (*a*) Rothbart, H. B.: Myasthenia Gravis in Children: Its Familial Incidence, J. A. M. A. **108**:715 (Feb. 27) 1937. (*b*) Hart, H. H.: Myasthenia Gravis with Ophthalmoplegia and Constitutional Anomalies in Sisters, Arch. Neurol. & Psychiat. **18**:439 (Sept.) 1927.

Laboratory Data.—The reactions to the Schick, Dick and Mantoux tests were negative. The Wassermann reaction of the blood of the patient and of the two parents were negative. Crystal clear fluid under normal pressure was obtained on spinal tap. The fluid showed 7 lymphocytes, 77 mg. of sugar and 723 mg. of chlorides per hundred cubic centimeters and no globulin. The Wassermann and the colloidal gold reaction of the spinal fluid were negative. The Jolly reaction of the muscles of the eyelids, the face, and the extremities was positive. The basal metabolic rate was +1 per cent on one occasion and zero on another. Normal structure was found on biopsy of a specimen from the left deltoid muscle, and there were no lymphocytic infiltrations. Both the relative and the absolute amounts of creatine and creatinine excreted in the urine in twenty-four hours were within normal limits on two determinations. The cholesterol content of the serum was 265 mg. per hundred cubic centimeters. Dextrose tolerance tests gave the following results: while fasting, 111 mg. of dextrose per hundred cubic centimeters of blood; one hour after ingestion of 100 Gm. of dextrose, 218 mg.; two hours later, 171 mg., and three hours later, 152 mg. Roentgen examination of the chest, the skull and the long bones revealed no abnormalities. No thymic enlargement was found. The electrocardiogram was normal. Examination of the blood showed the hemoglobin content was 12.8 Gm. per hundred cubic centimeters (88 per cent, Sahli). The red blood cells numbered 5,010,000 and the leukocytes 13,400 per cubic millimeters, with 75 per cent neutrophils and 25 per cent lymphocytes. Examinations of the urine gave normal results.

Course.—The child's muscular power varied greatly with the length of time that had elapsed between the preceding administration of prostigmine methylsulfate and the examination. On one occasion, when allowed to go for twenty-four hours without receiving the drug, she grew steadily weaker until she was quite helpless and apathetic. Her face became masklike, and her eyelids drooped heavily. Her speech became thick, nasal and somewhat explosive. She could speak a few words or count to twenty, but then she stopped, saying she was tired. She could barely lift her head off the pillow and could only feebly lift her arms above her head. Again after twenty-one hours had elapsed since she had received a dose of the drug, she began to complain of difficulty in respiration, although there were no outward signs of it. Shortly afterward, her breathing became labored and she had difficulty in swallowing even liquids. She became anxious, and her complaints of respiratory difficulty grew more insistent. Her jaw began to droop, and she supported it with her hands when attempting to speak. Then, suddenly, she became intensely cyanotic. The administration of 0.87 mg. of prostigmine methylsulfate subcutaneously brought about, in fifteen minutes, a marked change in her condition. The ptosis disappeared completely, and her speech became firm, fluent and but slightly nasal. She was able to get off her bed and to return to it with little aid. She could walk about the room and climb a few steps, although her gait was still hesitant. This period of increased muscular power lasted about two hours, after which weakness gradually reappeared.

With a daily dose of 0.75 mg. of prostigmine methylsulfate given subcutaneously or of 45 mg. of prostigmine bromide given by mouth, the child was kept comfortable and in good spirits. She had no respiratory distress, difficulty in deglutition or ptosis and could walk short distances. She was discharged Jan. 19, 1939, with instructions to take 45 mg. of prostigmine bromide by mouth, four times daily. After discharge, the prostigmine was discontinued, on the advice of a private physician. Weakness returned and was progressive.

Second Admission.—On February 3 the child was readmitted to this hospital, with marked respiratory difficulty and cyanosis. Prostigmine methylsulfate was administered hypodermically, and she was placed in a respirator, where she remained for nine hours.

Physical findings were essentially the same as on the previous admission, except that the pharynx was injected and that sibilant and sonorous rales were heard throughout the posterior portion of the chest. Pupillary accommodation could be fatigued after ten trials, and superficial reflexes were exhaustible. The temperature ranged between 100 and 101 F. for thirty-six hours, and the child was fairly comfortable. Respiratory failure then set in anew, and she was again placed in a respirator. The temperature mounted steadily to 106 F., and the child died at the end of seventy-two hours in the hospital. The administration of large doses of prostigmine methylsulfate during the last thirty-six hours was of no avail.

The final diagnosis was myasthenia gravis and bronchopneumonia. Permission for a postmortem examination could not be obtained.

COMMENT

Despite the increased interest in myasthenia gravis since the introduction of the newer forms of therapy, we were unable to find any reference in the literature to reviews of the condition in children. In standard pediatric reference works discussion is restricted to brief general statements. It is of interest, therefore, to present some of the salient features of the 34 cases of the condition in children which have been reported.

In the majority of cases reported, as in our case, the onset of symptoms of the disease was insidious. Prodromal symptoms of headache, pain and paresthesias in various parts of the body have been mentioned. While the order of evolution in various parts of the body of clinical manifestations due to muscular weakness differed in the various cases, fatigability and general muscular weakness and weakness of the ocular muscles comprised the initial complaints in 73 per cent of the cases. Fatigability and general muscular weakness were the first complaints in our case and in 19 cases in the literature. Symptoms referable to the eyes, such as ptosis, diplopia and general ophthalmoplegia, were present initially in 17 cases. Disturbances of speech and of deglutition on the other hand were found to be late-appearing symptoms. In 21 cases involvement of speech was present at some time during the course of the disease, but it was the presenting complaint in only 5 cases. Dysphagia occurred at some time in 20 cases and initially in 3. Dysphagia and nasal speech were present early in our case, while symptoms referable to the eyes were late in appearing.

Weakness of nonstriated muscles has been reported in a few cases. Markeloff [8] reported a case of sudden cardiac failure in an adult in which death was presumably due to involvement of the heart muscle.

8. Markeloff, C. I.: Die Myasthenia, Arch. f. Psychiat. **49**:482, 1912.

Foxe [9] reported the occurrence of cyclic intestinal atony, and McClean and Horton [10] reported an instance of postural hypotonia, which they attributed to involvement of the muscle coats of the arteries. On her second admission to the hospital, our patient showed fatigue of pupillary accommodation after about ten trials.

Lymphocytic infiltrations of skeletal muscles are generally considered a characteristic feature of the disease. Only one biopsy on a specimen of muscle has been reported, and the results were normal, as were those of a biopsy in our case. Milhorat and Wolff,[11] on the other hand, found lymphocytic infiltrations and nuclear proliferation in specimens of muscle taken post mortem in 1 of their cases. Enlargement of the thymus, which has also been considered to be associated frequently with myasthenia gravis, was reported in but 1 case, by Booth.[12] Roentgen studies in 5 cases, including our own, and postmortem examinations in another 5 cases failed to reveal thymic enlargement or any constant pathologic change.

Reports of chemical studies in cases of myasthenia gravis are conflicting. Rothbart [7a] reported an increased dextrose tolerance in 1 case. Our observations, however, were similar to those of Williams and Dyke [13] and Hart,[7b] who found that dextrose tolerance was diminished. Creatine-creatinine metabolism was reported to be altered in some cases but was normal in our case. The present status of knowledge concerning creatine-creatinine metabolism in patients with myasthenia gravis has been summarized admirably by Milhorat and Wolff,[11] who made studies of 11 patients. In most cases they found only moderate creatinuria and moderate impairment of creatine tolerance. In 2 rapidly fatal cases, however, the patients excreted large amounts of creatine. There was no appreciable difference between the patients' excretion of creatine during a remission and during an exacerbation of the disease, but in the latter phase the disturbance could be exaggerated by the administration of aminoacetic acid. Excretion of creatinine was found

9. Foxe, A. N.: Report of a Case of Myasthenia Gravis with Visceral Symptoms and a Clinical Contrast with a Case of Dystonia Musculorum Deformans, J. Nerv. & Ment. Dis. **68**:134, 1928.

10. McClean, A. R., and Horton, B. T.: Myasthenia Gravis with Postural Hypotension, Proc. Staff Meet., Mayo Clin. **12**:787 and 814, 1937; **13**:21, 1938.

11. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: III. Metabolism of Creatine and Creatinine in Myasthenia Gravis, Including a Study of the Excretion of Nucleosides and Nucleotides, Arch. Neurol. & Psychiat. **39**:354 (Feb.) 1938.

12. Booth, J. A.: Report of a Case of Myasthenia Gravis Pseudo-Paralytica with Negative Pathological Findings, J. Nerv. & Ment. Dis. **35**:690, 1908.

13. Williams, B. W., and Dyke, S. C.: Creatinuria and Glycosuria in Myasthenia Gravis, Quart. J. Med. **15**:269, 1922.

to be slightly or moderately diminished. Milhorat and Wolff expressed agreement with the belief of Adams, Power and Boothby [14] that the chemical changes in cases of myasthenia gravis are not uniform.

The value of administering prostigmine compounds to patients with myasthenia gravis has been well established in the literature. Unfortunately, however, the drug has not been in use sufficiently long to permit an evaluation of its influence on the ultimate course of the disease and on the duration of life. Administration of potassium chloride has been advocated as an adjuvant to prostigmine therapy, and recently Minot, Dodd and Riven [15] reported improvement in muscular function in patients with myasthenia gravis who were treated with guanidine hydrochloride. Viets and Schwab [16] analyzed their experience in administering prostigmine to 44 patients and have expressed the opinion that prostigmine bromide taken by mouth and supplemented with ephedrine sulfate, potassium chloride and, occasionally, guanidine is the most efficient form of treatment now available.

The total duration of the disease in our case was eighteen months, and the average duration in the 34 cases reported in children was forty-five and seven-tenths months. In 13 cases in children under 12 years of age, the average duration was fifteen months, and in 10 cases with fatal termination of the disease it was fifteen and six-tenths months. The duration of the disease in our case, therefore, was similar to that in other cases reported. Administration of prostigmine methylsulfate to our patient undoubtedly prolonged her life, however, for several months after attacks dyspnea had become frequent.

SUMMARY

A case of myasthenia gravis in a 9 year old child is presented, and the available data on 34 additional cases of the disease in children, gathered from the literature, are summarized. The clinical and pathologic features of the condition and the course are described, and the newer methods of treatment briefly discussed.

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14. Adams, M.; Power, M. B., and Boothby, W. M.: Chemical Studies in Myasthenia Gravis, Ann. Int. Med. **9**:823, 1936.

15. Minot, A. S.; Dodd, K., and Riven, S. S.: Use of Guanidine Hydrochloride in Treatment of Myasthenia Gravis, J. A. M. A. **113**:553 (Aug. 12) 1939.

16. Viets, H. R., and Schwab, R. S.: The Diagnosis and Treatment of Myasthenia Gravis, J. A. M. A. **113**:559 (Aug. 12) 1939.

OSTEOCHONDRODYSTROPHIA DEFORMANS (MORQUIO'S DISEASE)

REPORT OF THREE CASES

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PHILADELPHIA

Osteochondrodystrophia deformans, or Morquio's disease, is a skeletal disease starting probably during fetal life and characterized by (1) dwarfism, (2) deformities of the bones of the trunk and the extremities and (3) roentgen changes, consisting of absence of centers of ossification, destruction, rarefaction and proliferation involving all of the bones of the body except possibly those of the skull.

In 1929 Morquio [1] described a form of osseous dystrophy occurring in 2 of a family of 5 children and reported 2 additional cases in 1935. In 1931 Ruggles [2] described the roentgen findings in the bones in 8 similar cases, in 5 of which the condition was familial. Another case, that of a patient observed for more than seven years, was added in 1932 by Meyer and Brennemann.[3] During the past eight years at least 25 new cases have been recorded in the literature under the name either of Morquio's disease or of osteochondrodystrophia deformans.

In 1908 Drysdale and Herringham,[4] in a paper with the title "An Undescribed Form of Dwarfism" described the cases of 3 sisters who

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The American Philosophical Society gave financial support from the Daland Fund.

From the Philadelphia Institute for Medical Research, the Shriners' Hospital and the Philadelphia General Hospital, Pediatric Service of Dr. Edward Thorpe.

1. Morquio, L.: Sur une forme dystrophie osseuse familiale, Arch. de méd. d. enf. **32**:129 (March) 1929; **38**:5 (Jan.) 1935.

2. Ruggles, H. E.: Dwarfism Due to Disordered Epiphyseal Development, Am. J. Roentgenol. **25**:91 (Jan.) 1931.

3. Meyer, H. F., and Brennemann, J.: A Rare Osseous Dystrophy (Morquio), Am. J. Dis. Child. **43**:123 (Jan.) 1932.

4. Drysdale, J. H., and Herringham, W. P.: An Undescribed Form of Dwarfism Associated with a Spatulate Condition of the Hands, Quart. J. Med. **1**:103 (Jan.) 1908.

showed both deformity and dwarfism. Although the authors presented no roentgenographic evidence, it is possible that their cases belonged to the group described by Morquio. Between 1910 and 1915 several other cases resembling those of Morquio were described by Bankart,[5] Langmead[6] and Jaroschy.[7] Cases described as instances of familial rickets may likewise have been examples of oteochondrodystrophia deformans, since in many of those recorded in more recent literature at one time or another, the condition has been diagnosed as and the patient treated for rickets. It is also probable that certain others described prior to 1929 as cases of "atypical achondroplasia," "rachitic chondrodystrophy" and "atypical chondrodystrophy" were instances of osteochondrodystrophia deformans.

The patients in the 3 cases described here came to us at about the same time. Patient 2 was seen by one of us (J. R. M.) at another hospital and was referred to the Philadelphia Institute for Medical Research for study. In obtaining a detailed history from this patient, it was discovered that he had a first cousin who suffered from a similar condition. This patient was located and included in this study. The third patient was referred to us from another hospital, with a diagnosis of "atypical achondroplasia." The 3 children were admitted to the pediatric division of the Philadelphia General Hospital on Nov. 2, 1938 for complete study.

REPORT OF CASES

CASE 1.—The patient, N. P., was a 12 year old Italian boy. His parents, 4 sisters and 1 brother were living and well. There was no history of consanguinity. The only other instance in the family of an illness similar to that from which the patient was suffering was that of the patient reported on in case 2 in this paper. These patients were first cousins, their mothers being sisters. The patient was born by spontaneous delivery at term. The birth weight was purported to have been 12 pounds (5,443 Gm.). He held up his head at 2 months, sat up unsupported at 6 months and began to cut his teeth at 7 months of age. At the age of 8 months the patient contracted measles, which was complicated by bronchopneumonia. He was seriously ill for over six weeks. On recovery, the mother observed that the child was "pigeon breasted and knock kneed." A physician told the parents that the child suffered from rickets, but no improvement was noted after four months of antirachitic treatment. At 13 months of age, the patient fell from his bed to the floor. He was taken to another hospital, where the parents were told that he had suffered a broken back, although recent roentgen studies revealed no evidence of such a condition. He was put in a body cast for five months and was finally

5. Bankart, A. S. B.: Case of Achondroplasia, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **1**:155, 1913.

6. Langmead, F.: Case of Pseudo-Rachitic Achondroplasia, Proc. Roy. Soc. Med. **1**:22, 1915.

7. Jaroschy, W.: Zur Kenntnis des klinischen Bildes der Chondrodystrophia foetalis, Beitr. z. klin. Chir. **83**:379, 1913.

discharged wearing a spinal brace. At the age of 2 years he began to walk. He was definitely knock kneed; his gait was waddling and continued to be so until the age of 6 years, when he stopped walking entirely. He has since been completely confined to bed. The parents believe the patient stopped growing at the age of 5 years; in fact, they insist that his height has actually decreased. At 10 years of age the patient lost control of both vesical and anal sphincters and since then has continued to be incontinent of both urine and feces.

Physical Examination.—The child seemed happy and alert, though his mentality may not have been quite equal to that of a normal boy of 12 years. His height was 43 inches (109 cm.), the arm span 47 inches (119 cm.), the length from the vertex cranii to the pubis 20.5 inches (52 cm.), the length from the pubis to the bottom of the heel 22.5 inches (57 cm.), the circumference of the head 21.5 inches (55 cm.) and the weight 47 pounds (21.3 Kg.). The patient leaned forward in bed, supporting the weight of his trunk by leaning forward on his thighs and resting the palms of his hands on the mattress of the bed (fig. 1). He was able to turn in bed but was unable to stand. The neck was shortened, and the head

Fig. 1 (case 1).—N. P. at 12 years of age; height, 43 inches (109 cm.); weight, 47 pounds (21.3 Kg.).

seemed to rest directly on the shoulders. The face presented a definite posterior slant; the palpebral slits were narrow; the bridge of the nose was depressed, and the eyes were wide apart. There was a definite anterior bulge of the sternum (pectus carinatum), about the size of grapefruit, on which the chin rested, as well as a bilateral Harrison groove. The upper and lower extremities appeared relatively long as compared with the length of the trunk. There were extreme dorsal kyphosis, genu valgum and marked pronation of the feet. The ends of the long bones, especially of the humeri, the femurs and the tibias, were enlarged. The abdomen was protuberant. The achilles tendons were contracted, producing a bilateral equinus deformity.

Laboratory Data.—A summary of the results of various laboratory procedures relating to this child and to the other 2 patients is given in table 1. Morquio,[1] in his first contribution, reported a reduction in the serum calcium. However, for this boy and for our other 2 patients normal values (11.1, 10.8 and 11.0 mg., respectively, per hundred cubic centimeters) were obtained, which are in agreement with the observations of other investigators.

Roentgen Examination.—In table 2 are roentgenographic data for this patient and for our other 2 patients. Some of the more important roentgenograms of this child are reproduced in figure 2.

Neurologic Examination.[8]—There had been no arrest in mental development. The cranial nerves showed no dysfunction. The muscles of the upper extremities were flabby and underdeveloped; the power against resistance was weak throughout the body, in conformity with the bony deformity and the arrest in muscular development; the coordination and the tendon reflexes were normal. Flexion of the arms was weak and extension slightly better; the hands were held in complete wrist drop. The palms were flat, but the small muscles were fairly well preserved. The movements of the muscles innervated by the ulnar and the median nerves were weak. No definite fibrillations were seen anywhere, but a few sugges-

TABLE 1.—*Laboratory Data for Three Patients with Osteochondrodystrophia Deformans*

	N. P.	C. P.	J. S.
Urine	Normal	Normal	Normal
Erythrocytes, per cu. mm.	4,400,000	6,240,000	5,980,000
Leukocytes, per cu. mm.	6,700	11,000	10,000
Hemoglobin content, per cent	78	104	91
Wassermann reaction	Negative	Negative	Negative
Constituents of blood, mg. per 100 cc			
Sugar	102	72	72
Urea	11	12	16
Creatinine	1.2	1	1
Calcium	11.1	10.8	11
Phosphorus	5.2	5	5
Cholesterol	212	172	184
Phosphatase, Bodansky units per 100 cc.	2	5	2
Protein, Gm. per 100 cc.	6.5	6.3	6.7
Albumin, Gm. per 100 cc.	4.6	4.4	4.6
Globulin, Gm. per 100 cc.	1.9	2.1	2.2
Albumin-globulin ratio	2.4	2.1	2.2
Bleeding time, min.	2.5	1.0	1.0
Clotting time, min.	4.0	7.0	5.0
Basal metabolic rate, per cent	+22	....	+5

tive fibrillations were observed in the muscles of the shoulder girdle. The legs were flaccid but held in extension. The patient was almost entirely unable to move any segment of the lower limbs, but he could make feeble movements of abduction and flexion of the legs alone. The muscles of the thighs, especially the quadriceps, were wasted. The achilles reflexes were hyperactive. There was a fine, rapid ankle clonus bilaterally. Tapping the patellar ligament sometimes elicited a clonus of the quadriceps and sometimes a slight reflex response. A Chaddock sign was present on the right side and a Rossolimo sign bilaterally. Plantar stimulation, with the small toes separated from the large toe, sometimes produced a definite Babinski reaction on the right side and a partial reaction on the left. The abdominal reflexes were active; the cremasteric reflexes were present. On manipulation, a mass reflex developed, consisting of clonus of the thighs, erection and clonus of the penis and evacuation of the bladder and the bowels. The sense of touch was lost over the legs and the abdomen to about the level of the eleventh thoracic

8. Dr. Bernard Alpers examined the patients and rendered the reports which are quoted in this case and in case 3.

TABLE 2.—*Roentgenographic Data for Three Patients with Osteochondrodystrophia Deformans*

	N. P.	C. P.	J. S.
Head	Hydrocephalic; large sinuses; small, deepened sella turcica	Hydrocephalic; plates thin; sinuses small; nasal bones flattened; normal sella turcica, slightly deepened; mastoids sclerotic	Large and brachycephalic; plates thin; nasal bones depressed; sella turcica small and deep; delayed eruption of teeth
Vertebrae	Bodies flat, elongated; articular surfaces roughened; osteochondritis along margins; lower dorsal kyphosis, with wedging and deformities of bodies of dorsal vertebrae	Bodies flat, elongated and rarefied; osteochondritis of articular surfaces; dorsal kyphosis	Bodies flat and elongated; osteochondritis along anterior borders; widened neural arches and intervertebral foramens; dorsal kyphosis
Thorax	Ribs wide, flat and thin; narrow intercostal spaces; anterior protrusion of sternum	Ribs widened, flattened, lengthened and thinned; intercostal spaces narrowed; marked anterior protrusion of sternum	Ribs wide, flat and thin; narrow intercostal spaces; flaring and widening of lower part of thoracic cage; anterior curving of sternum but no pectus carinatum
Shoulders and upper extremities	Clavicles broadened; glenoid fossae shallow and irregular; humeral diaphyses shortened, ends broadened; humeral epiphyses honeycombed, epiphysial lines united; radial and ulnar diaphyses shortened, epiphysial lines united, ends of shafts irregular, rarefied and showing osteochondritic changes; 4 centers of ossification in left and 5 in right wrist; smaller bones shortened, thinned and trabeculated	Outer ends of clavicles broadened; scapulas small; humeral diaphyses shortened, metaphyses broadened; upper humeral epiphyses widened and rotated downward and inward, epiphysial lines irregular and narrow; lower humeral epiphyses irregular and united to shaft; ulnar and radial diaphyses short, ends broadened and articulating surfaces roughened; 3 carpal centers of ossification in right and 2 in left wrist; smaller bones shortened, thinned and trabeculated	Clavicles and scapulas small; glenoid fossae shallow; short diaphyses; metaphyses broadened, thickened and irregular; upper epiphyses large and honeycombed, epiphysial lines irregular; ulnar diaphyses larger than radial; lower metaphyses rough and broadened, with wide epiphysial lines, 6 centers of ossification in each wrist; smaller bones shortened, thinned, rarefied and trabeculated
Pelvis and lower extremities	Anthropoid pelvis; inward protrusion of acetabulums; osteochondritis in hip joint; capital epiphyses flattened, necks broadened; femoral diaphyses thinned, shortened and trabeculated; femoral epiphyses united, ends broadened and rarefied; upper portions of tibial and fibular diaphyses shortened and thinned; epiphyses irregular and rarefied; small bones of feet flattened, rarefied, thinned and trabeculated	Anthropoid pelvis; inward protrusion of acetabulums; femoral capital epiphyses fragmented and roughened; necks and femoral diaphyses shortened; femoral shafts thinned, rarefied and trabeculated, flattened and irregular; diaphyses of tibias and fibulas shortened and thinned, epiphyses irregular and flattened; lower epiphyses globular, with thickend margins; small bones of feet flattened, shortened, rarefied and trabeculated	Anthropoid pelvis; shallow acetabulums; bilateral coxa vara; capital epiphyses fragmented, sclerosed and honeycombed; femoral diaphyses thinned, rarefied and trabeculated; lower femoral epiphyses flattened, honeycombed and fragmented; tibial and fibular diaphyses shortened and upper and lower epiphyses flattened, rarefied and fragmented; articulating surfaces roughened; appearance of tarsal centers of ossification delayed; small bones of feet shortened, thinned, rarefied and trabeculated

segment. Sensations of heat and cold were lost to about the level of the tenth and the sensation of pain bilaterally to about the level of the eighth thoracic segment. The patient began to appreciate pain as an unpleasant sensation at about the level of the tenth thoracic segment but did not recognize it as pain until about the level of the sixth thoracic segment.

"*Impression.*—This boy has evidence of muscular atrophy, weakness of the arms and loss of reflexes, except the achilles, but no fibrillations. He has disease

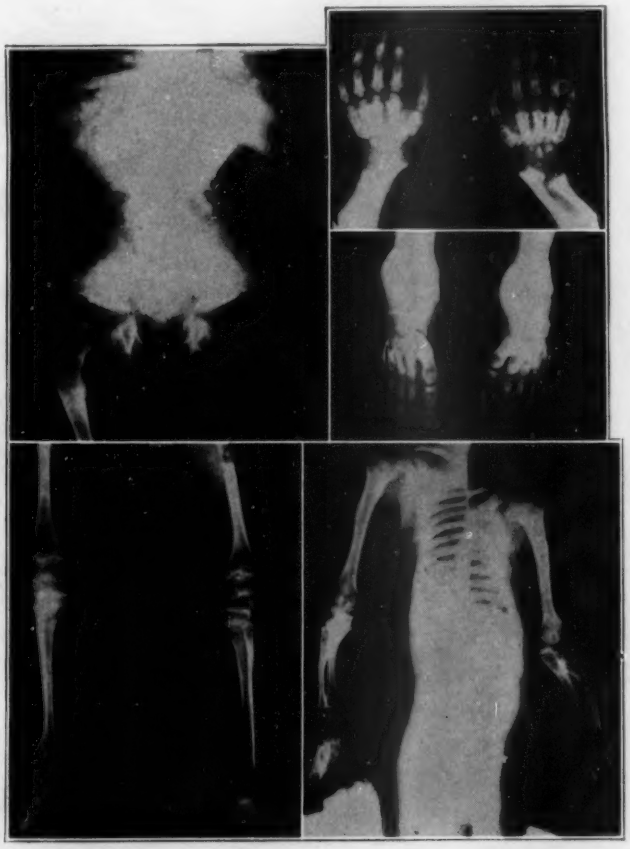

Fig. 2 (case 1).—Roentgenograms of N. P., aged 12 years.

both of the posterior columns of the spinal cord and of the pyramidal tracts, which involves the legs and a sensory level extending from about the sixth thoracic to about the twelfth thoracic segment, depending on the various sensations involved. He probably has, therefore, a transverse lesion which is due to compression over several segments in the lower thoracic portion of the spinal cord. The compression may be the result of kyphosis or of narrowing of the spinal canal but is not the result of primary disease of the spinal cord. The involvement of the arms is probably the result of faulty osseous development, although the muscular wasting and weakness are greater than can be explained on this basis. It is conceivable,

therefore, that there may be intrinsic changes involving the cervical portion of the cord."

CASE 2.—The patient, C. P., was a 7 year old Italian boy. The parents and a younger sister were living and well. The mother of this patient and that of N. P. (case 1) were sisters. There was no other history of similar illness or of consanguinity in the family. The patient was born at term by spontaneous delivery; the birth weight was 4½ pounds (2,041 Gm.). He held his head up at 3 months, began to cut his teeth at 8 months, sat up with support at 12 months and walked at 3 years of age. At 3 months of age, he was treated in another hospital for bilateral clubfoot. At 1 year of age, the mother observed that protrusion of the chest and curvature of the spine were developing. Aside from frequent infections of the upper respiratory tract, this patient had none of the usual diseases of childhood. At the age of 4 years he lost the use of his legs and has since been completely confined to bed.

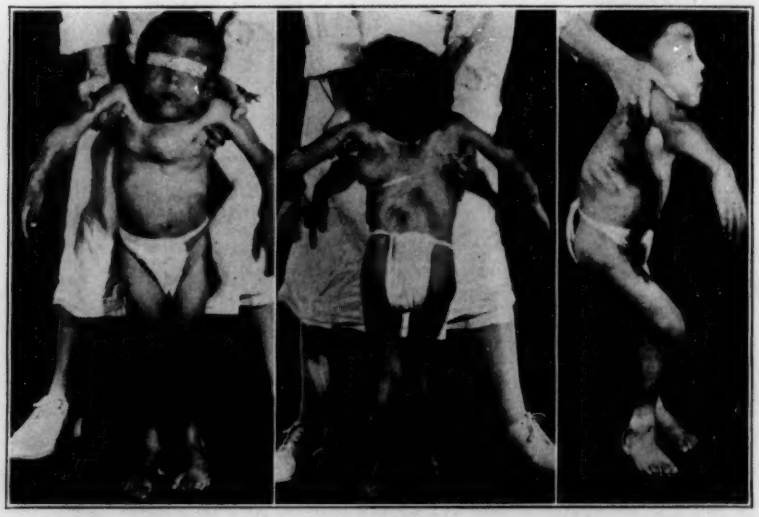

Fig. 3 (case 2).—C. P. at 7 years of age; height, 37 inches (94 cm.); weight, 36 pounds (16.3 Kg.).

Physical Examination.—The child was alert, happy and of normal mentality. The height was 37 inches (94 cm.), the arm span 40 inches (102 cm.), the length from the vertex cranii to the pubis 20 inches (76 cm.), the length from the pubis to the bottom of the heel 17 inches (43 cm.), the circumference of the head 23¾ inches (60 cm.) and the weight 36 pounds (16.3 Kg.). The patient was able to sit up and turn in bed but was unable to stand. He was obviously a deformed dwarf, with a large oval head flattened laterally and a short neck; the head seemed to rest directly on the shoulders (fig. 3). The bridge of the nose was flat, and the eyes were wide apart. The palpebral fissures were angular and slanting and suggested the facies seen in persons with mongolism. As in the other cases, the upper and lower extremities appeared relatively long as compared with the length of the trunk. There were marked dorsolumbar kyphosis and a definite anterior bulge of the sternum (pectus carinatum), about the size of an orange, on which the chin rested. There were extreme genu valgum and pes

planus. The ends of the long bones, particularly of the shoulders, the elbows, the wrists, the ankles and the knees, were widened. The anteroposterior diameter of the chest was increased; the abdomen was protuberant. The patient sat in bed with his trunk flexed on his thighs, supported by his thighs. Both achilles tendons were contracted, producing a bilateral equinus deformity.

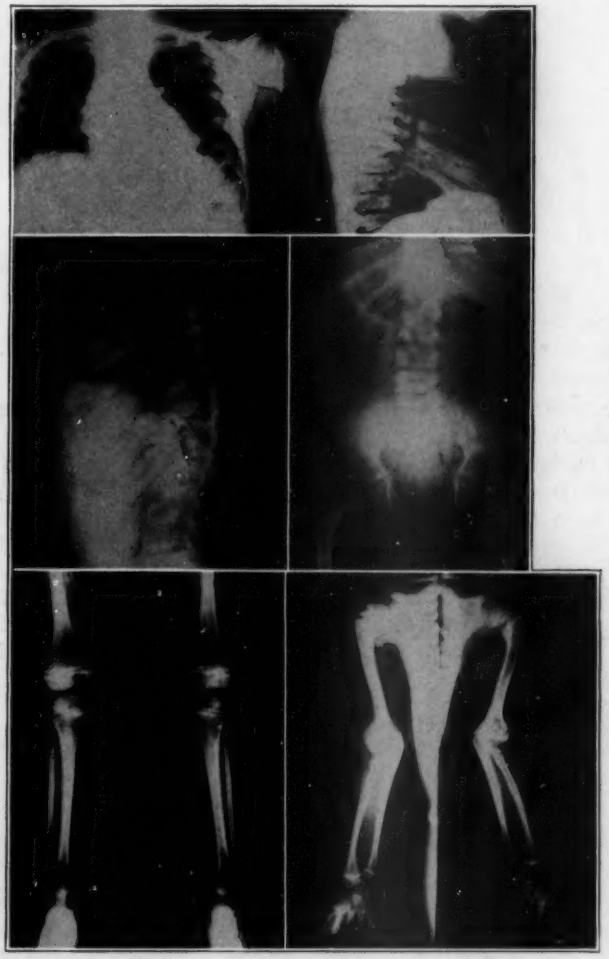

Fig. 4 (case 2).—Roentgenograms of C. P., aged 7 years.

Roentgen Examination.—The data are summarized in table 2. Some of the more important roentgenograms of this patient are reproduced in figure 4.

Neurologic Examination.[9]—The head was peculiarly shaped, with an increase in the occipitofrontal diameter. The eyes were almond shaped; the nose was small and flat, suggestive of the type seen in persons with mongolism. The pupils were equal and regular and reacted to light; there was slight paresis of the right

9. Dr. B. Weiss examined the patient and rendered the neurologic report.

external rectus muscle; the other ocular muscles were unimpaired. There was no nystagmus or weakness of the face, the palate or the tongue. The upper extremities were flaccid; wrist drop was present bilaterally. There was atrophy of the thenar and hypothenar eminences and, to a lesser degree, of the muscles of the arm, the forearm and the shoulder girdle. The grip was practically nonexistent, there being only a slight amount of power in the upper limbs. There was no fibrillation. The right biceps reflex was hyperactive and the left absent. The triceps and wrist reflexes were active bilaterally; Trömner's sign was absent. The muscles of the back were not involved. The abdominal and cremasteric reflexes were hyperactive. The patient lay with the lower extremities semiflexed and the feet everted. There was complete absence of plantar and dorsal flexion of the feet. He could elevate his extremities 6 or 8 inches (15 or 20 cm.) above the bed. There was slight atrophy of the thigh and the gastrocnemius group of muscles. There was bilateral increase of tonicity, somewhat more marked on the left side. There were ankle clonus and Babinski and Chaddock signs bilaterally. The knee and ankle jerks were hyperactive; patellar clonus could not be elicited. The sense of pain was unimpaired.

"Impression.—The patient presents evidence of flaccid paralysis of the upper limbs, with atrophic musculature and increased tendon reflexes, except for that of the left triceps, together with pathologic changes in the spinal cord."

Chemical and Histologic Examination of Muscle and Bone.—With use of local anesthesia, a specimen of muscle and bone was removed from the lower portion of the left femur for chemical and histologic study. Dr. James H. Jones, of the department of physiologic chemistry of the University of Pennsylvania, rendered the following report:

	Percentage
Moisture	26.8
Lipids	23.3
Bone ash (dry, lipid-free bone)	54.2
Calcium	37.3
Phosphorus	16.48

These results can be considered normal, with the possible exception of the value for phosphorus, which is about 2 per cent below that found for the rat by Hammett.[10] Several attempts were made to determine the amount of magnesium, but because of the small amount of material at hand the results were not reliable.

Dr. J. G. Reinhold, of the department of chemistry of the Philadelphia General Hospital, studied the specimen of muscle and submitted the following report:

	Calculated Value, Mg./100 cc.	Normal Value, Mg./100 cc.
Creatine	322	400
Total acid-soluble phosphorus	133	165
Creatine phosphorus	2.42	2.4
Chloride	140	50

Comparison of these determinations with the normal values shows that all of the constituents are within normal limits except the chloride, which is greatly increased.

10. Hammett, F. S.: Biochemical Study of Bone Growth: Changes in Composition of Ash During Growth, J. Biol. Chem. **64**:693 (July) 1925.

What significance this may have other than to suggest an increase in the connective tissue phase to two or three times the normal cannot be stated.

Dr. R. P. Custer, formerly of the department of pathology of the Philadelphia General Hospital, rendered the following histologic report on the specimen of muscle and bone:

"A. The section was taken through voluntary muscle and attached fascia. The muscle fibers display a greater scatter in width than is usual and are in general slightly smaller than normal. Longitudinal fibrils and cross striae are distinct; the sarcoplasm is fairly evenly and deeply stained. There is no replacement by fat or fibrous tissue. The diagnosis is mild atrophy of the voluntary muscle.

"B. The articular cartilage appears to have undergone retrogressive change, evidenced by loss and degeneration of the bulk of chondrocytes and vague focal

Fig. 5 (case 3).—J. S. at 7 years of age; height, 39 inches (99 cm.); weight, 38 pounds (17.2 Kg.).

vacuolation of the interstitial material. There is almost complete loss of subchondral bone, the marrow beneath being sparsely trabeculated; the adjacent cortical bone seems to be discontinuous as well. There is no evidence of active bone resorption at the moment, and no osteoblastic proliferation is observed. The diagnosis is degeneration of the articular cartilage and atrophy of the periarticular and the subchondral bone."

CASE 3.—The patient, J. S., was a 7 year old Polish boy. His parents, 2 older brothers and 1 sister were living and well. There was no history of consanguinity or of any illness in other members of the family similar to that from which the patient suffered. He was born at term, by spontaneous delivery; the birth weight was 7 pounds (3,175 Gm.). He began to cut his teeth at 6 months, sat unsupported at 10 months and began to make efforts at standing at 12 months of age. At the age of 18 months the patient was thought to have rickets and received antirachitic therapy in another hospital. At the age of 3 years he began

to walk. He contracted varicella and scarlet fever at 4 years and measles at 6 years of age. His tonsils and adenoids were removed at 6 years of age. Before coming under our observation, he had been treated in several hospitals for such conditions as achondroplasia, arthritis and congenital dislocation of the hip.

Physical Examination.—The height was 39 inches (99 cm.), the arm span 42 inches (107 cm.), the length from the vertex cranii to the pubis 21 inches (53 cm.), the length from the pubis to the bottom of the heel 18 inches (46 cm.), the circumference of the head 20¾ inches (53 cm.) and the weight 38 pounds (17.2 Kg.). The intelligence was normal. The gait was waddling and suggested congenital dislocation of the hip. The most striking features were the length of the lower extremities, the shortness of the neck, the trunk and the upper part of the

Fig. 6 (case 3).—Roentgenograms of J. S., aged 7 years.

arms, the dorsal kyphosis and the moderate lumbar lordosis, the widening of the hips, the prominence of the trochanters, the genu valgum and the marked pronation of the feet (fig. 5). The ends of the long bones were abnormally enlarged, especially the lower ends of the tibias, the fibulas and the femurs. The trochanters were definitely above Nélaton's line; there was a positive, bilateral Trendelenburg reaction; the hip was stable. The head seemed large; the nose was depressed; the position of the eyes was normal and the neck was short. The anteroposterior diameter of the thoracic cage was increased. There was a slight forward bulge of the sternum, although not as marked as that observed in cases 1 and 2. The abdomen was protuberant.

Roentgen Examination.—The data are summarized in table 2. Some of the patient's more important roentgenograms are reproduced in figure 6.

Neurologic Examination.—The pupils were equal and regular, and reacted promptly to light and in accommodation. The fundi were normal, the corneal

reflexes active and the ocular movements normal in all directions. The masseter and temporal muscles were normal. No weakness of the face, the palate or the tongue was observed. The biceps and the triceps muscles were small. The muscles of the forearm were also decreased in size. The power of the biceps and the triceps was definitely less than that of the muscles of the shoulder girdle. Pronation and supination of the forearm were weakened. The grip of the hand was inadequate. Flexion and extension of the wrists were powerful. There was flattening of the dorsum of both hands, with beginning flattening of the palms. There was good movement of the small muscles of the hands. There was definite weakness of extension of the thighs and of flexion and extension of the legs. Dorsal and plantar flexion of the feet was weak; both feet were held in the position of foot drop. The lower parts of the thighs tapered off, and the left quadriceps muscle was definitely decreased in bulk. The gastrocnemius, tibial and peroneal groups of muscles were wasted; no fibrillations were seen anywhere. The biceps and the triceps reflexes were absent. The knee and the ankle jerks were decreased. Plantar stroking caused extension of the right big toe, but there was no Babinski sign on the left. There was no ankle or patellar clonus and no Chaddock or Rossolimo sign. The reactions to heat, cold and touch were normal.

"*Impression.*—The impression made by this boy is in marked contrast to that made by the patient in case 1, for he shows well rounded muscular contour instead of excessive atrophy. However, he already has some wasting of the muscles of the arms and the legs, with a proportionate loss of power. In addition, he has changes in the reflexes. It appears that the muscular disturbance is progressing concurrently with the osseous development, but the absence of reflexes indicates that there must be some interference with the nerves or with the anterior horn cells."

Diagnosis.—Doubt still exists in the mind of one of us as to the exact diagnosis in this case. However, it should be recorded that it was through the suggestion of Dr. F. W. Glenn that we considered the possibility that this patient had osteochondrodystrophia deformans and recognized the presence of this disease in the other 2 patients.

COMMENT

In 1921 Morquio [1] described the cardinal manifestations of the disease which has since come to bear his name but which, as suggested by Shelling,[11] is probably better known as osteochondrodystrophia deformans. Translating rather freely from Morquio's original communication, one reads:

These manifestations are chiefly painless bony changes which affect the body, vertebral column and extremities, sparing the head and face, and which give rise to functional as well as physical problems affecting motility. The skeletal deformities are generalized and consist of the following abnormalities: (1) bony exuberances in the sternum, vertebral column and epiphyses of the shoulder, elbows and knees; (2) retardation or absence of ossification, particularly in the wrists, hands, ankles and feet, and (3) relaxation of the ligaments and periarticular muscles, particu-

11. Shelling, D. H.: Osteochondrodystrophia Deformans, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 4, chap. 29.

larly in the hands and feet, resulting in genu valgum, pes planus, difficult gait and marked diminution in the strength of the hands and feet, without apparent muscular atrophy or altered electrical reactions. Thus the whole body presents marked deformity characterized by longitudinal shortening. There is anteroposterior deepening of the thorax, with the sternum projecting to a point (pectus carinatum); the extremities, though deformed, have normal dimensions, and the appearance is that of children suffering from Pott's disease with an extensive cicatricial gibbus. The intelligence is normal. Roentgen examination reveals a profound alteration in osteogenesis consisting in rarefactions, malformations and destruction, retardation and absence of centers of ossification, more or less complete, in the extremities, but affecting particularly the epiphyses of all the long bones.

In our opinion, of the 40 odd cases described in the literature,[12] the condition in 35 conforms to Morquio's original description.[10] The remaining few, as well as a number described before 1929 which are often cited, may not be true instances of osteochondrodystrophia deformans. At least they must be regarded as being atypical. The atypical features may be grouped under the following headings: (1) obesity, nanism,[13] (2) local malacias of the shoulder and hip joints, resembling Perthe's disease,[14] (3) mental retardation and general enlargement of

12. Valentin, B.: Knochensystemerkrankung (Atypische Chondrodystrophie, Osteochondropathia multiplex) und sogenannte Platyspondylia generalisata, Zentralbl. f. Chir. **57**:2038 (Aug. 16) 1930. Dale, T.: Unusual Forms of Familial Osteochondrodystrophy, Acta radiol. **12**:337, 1931. Campbell, D.: Ueber eine typische Form des Zwergwuchses infolge gestörter enchondraler Ossifikation und die Frage ihrer Verwandtschaft mit der Chondrodystrophie, Röntgenpraxis **3**:751 (Aug. 15) 1931. Brown, D. O.: Morquio's Disease, M. J. Australia **1**:598 (May 13) 1933. Barnett, E. J.: Morquio's Disease, J. Pediat. **2**:65 (June) 1933. Coward, N. R., and Nemir, R. L.: Familial Osseous Dystrophy (Morquio's Disease), Am. J. Dis. Child. **46**:213 (July) 1933. Ellman, P.: A Rare Primary Osseous Dystrophy, Brit. J. Child. Dis. **30**:188 (July-Sept.) 1933. Summerfeldt, P., and Brown, A.: Morquio's Disease: Report of Two Cases, Arch. Dis. Childhood **11**:221 (Aug.) 1936. Guérin, R., and Lachapèle, A. P.: Chondrodystrophie avec élargissement et diminution de hauteur des vertèbres (platybrachyspondylie), Rev. d'orthop. **25**:23 (Jan.) 1938. Freeman, J.: Morquio's Disease, Am. J. Dis. Child. **55**:343 (Feb.) 1938. Gamboa, M., and Salvati, A. A.: Osteocondrosis generalizada; enfermedad de Morquio, Rev. Asoc. méd. argent. **52**:551 (June 30) 1938. Marottoli, O. S., and de Azcuénaga, S.: Osteocondrodistrofia generalizada; enfermedad de Morquio, An. de cir. **4**:387 (Dec.) 1938. Comby, J.: La maladie de M. Morquio, Arch. de méd. d. enf. **42**:37 (Jan.) 1939. Pohl, J. F.: Osteodystrophy (Morquio's Disease): Progressive Kyphosis from Congenital Wedge-Shaped Vertebrae, J. Bone & Joint Surg. **21**:187 (Jan.) 1939. Crawford, T.: Morquio's Disease, Arch. Dis. Childhood **14**:70 (March) 1939. Jacobsen, A. W.: Hereditary Osteochondrodystrophia Deformans (Morquio's Disease): Family with Twenty Members Affected in Five Generations, J. A. M. A. **113**:121 (July 8) 1939.

13. Grenet, H., and Isaac-Georges, P.: Sur un état dystrophique complexe de l'enfance, Arch. de méd. d. enf. **38**:725 (Dec.) 1935.

14. Silfverskiöld, N. A.: Sur la question de l'achondroplasie atypique et de sa forme péripherique, Acta radiol. **5**:223, 1926.

the joints,[15] (4) gargoylism, congenital clouding of the cornea, hepatosplenomegaly and mental retardation,[16] (5) alteration in the size and the shape of the head, shortness of all four limbs and a normal trunk.[17]

As is universally the case in diagnosis, little difficulty is encountered once the disease is fully established, while more or less uncertainty attends its recognition in the early stages. It is apparent from the literature and from the 3 cases presented in this communication that there is no group of classic, early manifestations which characterizes the condition in all of the cases. In many instances the disease is first observed when the child begins to stand or walk. At this time, the parents may note slight kyphosis, enlargement of such joints as the elbows, wrists, knees and ankles or anterior protrusion of the sternum. Some of these observations are suggestive of rickets; in fact, it is surprising to note in how many of the reported cases the first diagnosis was that of rickets. The deformities noted, however, continue to grow more severe in spite of adequate antirachitic therapy.

The clinical features of a case of well developed osteochondrodystrophia deformans are pathognomonic, so that it may be recognized at a glance by the physician familiar with the condition, just as he will recognize the fully established picture of exophthalmic goiter, acromegaly or Paget's disease. The final picture is essentially that of a dwarf with a normal-sized head lodged low between the shoulders on a short stubby neck and resting on a box-shaped torso, an anterior protrusion of the sternum which forms a shelf on which the chin seems to rest, dorsal kyphosis and deformed, more or less useless limbs attached as dangling appendages.

The greatest help in establishing a correct diagnosis is derived from roentgenologic studies. The epiphyses of the long bones are usually irregular, enlarged, flattened and of varying density, suggesting cellular destruction; the heads of the femurs may be absent, misshapen or fragmented; the glenoid fossae or acetabulums may be irregular, so that articulation with the heads of the articulating bone is improper; the

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15. Thursfield, H.: General Enlargement of Joints, Proc. Roy. Soc. Med. **18**: 42, 1924. Warkany, J., and Mitchell, A. J.: Atypical Chondrodystrophy, J. Pediat. **4**:734 (June) 1934. Giraud, G., and Bert, J. M.: La dystrophie osseuse de Morquio dans le cadre des hyperlaxités familiales, Rev. neurol. **63**:845 (June) 1935.

16. Ellis, R. W. B.; Sheldon, W., and Capon, N. B.: Gargoylism, Chondro-Osteodystrophy, Corneal Opacities, Hepato-Splenomegaly, and Mental Deficiency, Quart. J. Med. **5**:119 (Jan.) 1936. Poynton, F. J.; Lightwood, R. C., and Ellis, R. W. B.: Hepatosplenomegaly with Mental Deficiency and Bone Changes, Proc. Roy. Soc. Med. **27**:1025, 1934. Cockayne, E. A.: Gargoylism (Chondro-Osteo-Dystrophy, Hepatosplenomegaly, Deafness) in Two Brothers, ibid. **30**:104, 1936. Davis, D. B., and Currier, F. P.: Morquio's Disease: Report of Two Cases, J. A. M. A. **102**:2173 (June 30) 1934.

17. Drysdale and Herringham.[4] Langmead.[6]

diaphyses are thinned and show areas of uneven density or rarefaction, particularly toward the ends; the cortices may be thickened on the side of the greatest strain. The small bones of the hands and feet are generally shortened and show thinning, irregularities of the epiphyses and increased trabeculation. The centers of ossification of the carpal and tarsal bones are usually deficient for the chronologic age. The bodies of the vertebrae are flattened and irregular in outline, with roughened articular surfaces and frequent wedging. Kyphosis in the dorsal and lumbar regions and thickening of the intervertebral disks are usually present. The ribs are widened and flat, and the intercostal spaces are narrowed, with anterior protrusion of the sternum of varying degree.

It is well to attempt to gain some insight into the pathogenesis of the various cardinal signs and symptoms of the disease. Dwarfism may be extreme, so that many of the victims of the disease do not exceed 45 inches (114 cm.) in height. The obvious explanation of the tardiness in growth is to be found in the following factors: (1) the underdevelopment and flattening of the bodies of the vertebrae, with resultant kyphosis, lordosis and pectus carinatum; (2) the shortening of the neck, due to flattening of the cervical vertebrae, and (3) the crouching position assumed by the patient, the genu valgum and the pes planus (figs. 1, 2 and 3). Certainly the combination of these factors can account for much of the actual shortening of the body. This explanation, however, may not account for all of the retardation in growth observed. Roentgen studies of the centers of ossification show absences, as well as retardation in their appearance, so that actually there may be an additional factor, possibly endocrine in nature, which affects development. In our 3 cases there were no demonstrable evidences of endocrine disorder: Roentgenograms of the sella turcica were normal in each case; the eyegrounds were normal; the basal metabolic rate was elevated in 1 instance, but it probably did not represent a true value because of the marked deformity of the patient; the determinations of calcium and phosphorus (in blood and in bone) were within normal limits, and the external genitalia were normally developed. The inclusion of endocrine dyscrasia as a factor in the causation of the dwarfism is not justifiable with the information available. Additional evidence should be sought.

The muscular weakness and physical disability are so profound that a child of 12 years may lack the strength of an infant of 2. For 2 of our patients walking, or even standing, was impossible. As one studies the movement of the joints, one is impressed with the marked restriction present. In view of the degree of flabbiness of the muscles and the relaxation of the ligaments, the logical inference is that this decreased mobility of the joints is due to the extensive changes which occur in their surfaces.

From an orthopedic point of view, Morquio's disease presents a group of interesting deformities, namely: pes planus, genu valgum, coxa vara, scoliosis, kyphosis, pectus carinatum, mild clubhand, humerus varus and skeletal dwarfism. They are due to structural defects, to postural changes and to a combination of the two. The structural alterations are covered adequately by the heading osteochondrodystrophia deformans. As is admirably demonstrated in cases 1 and 2 here reported, the postural changes are secondary to the structural and neurologic alterations.

Careful study of these 2 cases makes it obvious that there are two distinct phases of this disease: first, that in which structural defects accompanied by postural changes occur and, second, that in which neurologic features become manifest. With the appearance of the second phase, the entire course of the disease is altered; the child becomes completely bedridden and eventually helpless. The changes in the bones in themselves do not account entirely for this new picture. One must look elsewhere for another, more plausible, explanation, possibly in the nature of a mechanical factor. Much to our surprise, definite platybasia was discovered in C. P., the only 1 of our patients studied from this point of view. This observation was confirmed by Dr. W. Edward Chamberlain, roentgenologist at Temple University, and may be of the utmost significance, since it would bring the neurologic changes encountered in patients with this disease in line with those seen in persons with multiple sclerosis or amyotrophic lateral sclerosis, which, according to the belief expressed by Dr. Chamberlain, are related to platybasia. Unfortunately, the parents of this patient refused to permit decompression of the foramen magnum and the first cervical vertebra. Hence, this opportunity to relieve the critical, and possibly fatal, phase of the disease was lost.

Polycythemia was noted in 2 cases. For N. P., whose disease was the most advanced of the 3 patients, the average erythrocyte count was only 4,400,000 per cubic millimeter, while for J. S., whose disorder was the least advanced, or mildest, the erythrocytes numbered 5,980,000. For C. P. the erythrocyte count was 6,240,000. It is, therefore, difficult to determine whether these observations are merely chance occurrences or are due to compensatory phenomena incident to the extreme deformity of the chest, with compression of the lungs and faulty aeration.

The diagnosis of osteochondrodystrophia deformans in the early stages is not easy. However, in the advanced stages the diagnosis of the disease frequently can be made at a glance. Morquio's disease is most often confused with the rickets of infancy, late rickets and renal rickets, as well as with chondrodystrophy. In 2 of our cases the disease was first diagnosed as rickets, and in many of those recorded in the literature a similar diagnosis was made and the patients received intensive

antirachitic therapy. After the failure of this therapy, more thorough study usually revealed the true nature of the disease. These errors usually result when the diagnosis is made without resort to a thorough roentgen examination. In order to clarify the important differences between osteochondrodystrophy, chondrodystrophy and rickets, the cardinal features of these three conditions are summarized in table 3, and photographs of patients with the three disorders are reproduced in figure 7.

It is unfortunate that to date there exists no detailed necropsy report on a patient with osteochondrodystrophia deformans. Obviously, the observations in one typical case would prove extremely illuminating. Under present conditions surmise rather than knowledge influences the physician's clinical judgment.

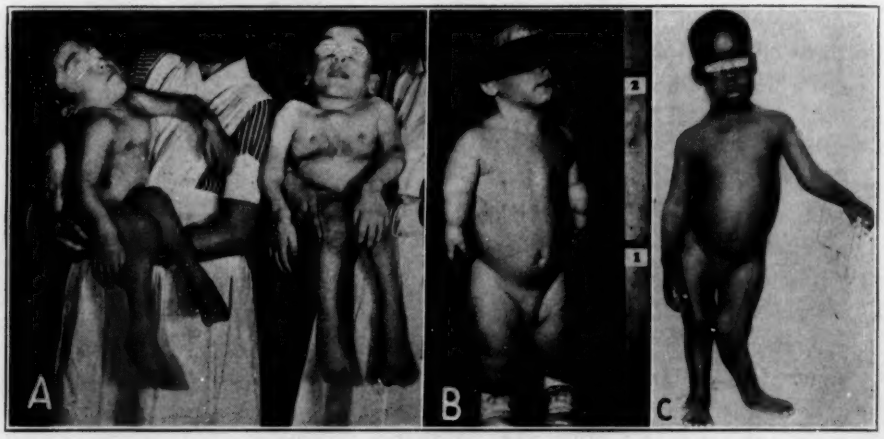

Fig. 7.—Clinical appearance of patients with well developed disorders. *A*, osteochondrodystrophia deformans; *B*, chondrodystrophia, and *C*, rickets.

It may be truthfully stated that there is no known treatment for osteochondrodystrophia deformans. Administration of thyroid preparations of the anterior lobe of the pituitary and the vitamins have been tried, but did not alter the course of the disease. It seems, however, that orthopedic care may offer a great deal in preventing or correcting the deformities of the back and extremities. If the case of J. S., our third patient, is accepted as an example of this disease and if his condition is compared with that of the other 2 patients, one cannot but feel that he is headed for a similar helpless existence. Is it possible to save him from this horrible state by constant orthopedic supervision? Only time can answer this question.

A second consideration may be worthy of mention. Is it possible to increase growth in these patients through the use of pituitary extracts

TABLE 3.—*Points of Differentiation of Osteochondrodystrophia Deformans, Chondrodystrophia and Rickets*

	Osteochondrodystrophia Deformans	Chondrodystrophia	Rickets
Causation and pathologic features	Exact cause unknown; probably related to chondrodystrophia and due to a developmental defect of ossifying cartilage; often familial, hereditary; consanguinity may be a factor. Nature of pathologic lesion surmised from biopsy and roentgen studies; probably a dyschondroplasia or variant of achondroplasia	Originates in fetal life; result of an arrest or faulty development of the primordial bone cartilage; may be familial, hereditary; consanguinity not a factor. Pathologic lesion consists essentially of retarded growth of long bones, due to defective growth of their cartilaginous ends	A deficiency disease resulting from lack of vitamin D in the diet, insufficient exposure to ultraviolet rays, deranged calcium and phosphorus metabolism. Pathologic lesion consists essentially of development of imperfectly calcified osteoid tissue, with resultant formation of soft bone
Clinical findings	No change observed at birth. Extent of deformities varies. Head appears large; root of nose depressed; eyes widely separated; neck shortened, with head resting on shoulders; trunk poorly developed, dorsal or lumbar kyphosis, anterior protrusion of sternum (pectus carinatum)—all producing shortened trunk; extremities slightly shortened; epiphyses of long bones enlarged, irregular and deformed; joint mobility depends on amount of change in joints; muscles and ligaments weak; strength of limbs reduced; coxa vara, genu valgum, pes planus; waddling gait, crouching position; mentality and sexual development normal	Changes observed at birth. Extent of deformities varies. Head large; bridge of nose depressed; prognathism; trunk well developed, with well formed, shortened and often bent extremities (micromelic dwarfism); epiphyses of long bones enlarged, often interfering with joint motion; musculature strong; insertions of muscles widened; coxa vara, genu varum; waddling gait; trident hand, fingers uniform in length; lumbar lordosis or kyphosis, pigeon breast frequent; mentality normal; sexual overdevelopment frequent	No changes observed at birth. Extent of deformities varies. Head square, with frontal bossing, anterior fontanel open; areas of softening in skull; delayed and defective dentition; trunk well developed; occasional kyphosis; thorax slightly deformed; enlarged costochondral junctions; Harrison's groove; abdomen protuberant; epiphyses of long bones, especially wrists, enlarged; muscles weak and flabby; joints relaxed; genu valgum and genu varum due to bending and twisting of bones
Roentgen findings	Profound alteration in osteogenesis, with rarefactions, malformations, destructions, retardations and absences affecting all the bones except possibly those of the skull; vertebral bodies broad and flat, with roughened articular surfaces; intervertebral disks roughened and flattened	Ends of bones broad and irregular; shafts short; epiphysial centers of ossification appearing early and uniting with shaft early; periosteum remaining intact, so that shafts are of normal width; metacarpal bones equal in length; pelvis flattened; vertebrae often wedge shaped; articular surfaces roughened	Bony changes due primarily to defective calcification and extensive proliferation of epiphysial cartilages. Cupping of cartilage-shaft junctions, especially in fibula and ulna; spreading and fraying of shaft ends of the bones; stippling and spur formation, especially at costochondral junction of ribs, radius and ulna
Blood chemical constituents	Inorganic phosphorus, calcium, sugar, phosphatase and cholesterol of serum normal	Inorganic phosphorus, calcium, sugar, phosphatase and cholesterol of serum normal	Inorganic phosphorus and calcium of serum decreased; phosphatase increased

containing the growth-promoting factor of the anterior lobe, supplemented with proper diet and administration of vitamins? As there exists some evidence that growth may be stimulated in patients with chondrodystrophy, it seems rational at least to attempt to accelerate growth of patients with osteochondrodystrophia deformans through the use of extracts containing the growth-stimulating principle.

SUMMARY

Records together with the results of study of 3 cases of osteochondrodystrophia deformans are presented.

Problems relating to diagnosis and to the pathogenesis of some of the clinical manifestations of this disease are discussed. Attention is called to the possible role of platybasia in the causation of the neuromuscular phenomena.

Progress in Pediatrics

GLYCOGEN DISEASE

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The recent historical review by van Creveld [1] of the cases reported as examples of glycogen disease not only called attention to the syndrome but demonstrated the great variation in the clinical and pathologic observations. These variations are indeed so great that it is reasonable to doubt whether the cases belong to a single disease entity. The concept has been that the fundamental basis of the disease is the inability of the liver or the heart to break down glycogen, and some cases can logically be interpreted on that basis. In others of the reported cases, however, the liver released dextrose on the administration of epinephrine, and postmortem studies showed the liver tissue to be capable of breaking down glycogen. The inclusion of these cases under the heading of von Gierke's disease has obscured the problem. It seems probable that the cases reported as examples of von Gierke's disease or of glycogen storage disease are not identical in pathogenesis but form a group which have in common several characteristics, namely, early onset, hepatomegaly and some abnormality of carbohydrate metabolism, the specific abnormality varying in different cases. It may be expected that further observations will result in the separation of several distinct disease entities from this group. In view of the general confusion of the subject, it appears to be of value to report a case in which the clinical and pathologic evidence points not only to a defect in the enzyme system of the liver which is responsible for the breakdown of glycogen into dextrose, but to the inability of the liver to form glycogen from dextrose. A critical analysis of the reported cases of glycogen storage disease and an attempt at classification on the basis of functional abnormality are also presented.

REPORT OF A CASE

S. L. was born in Sloane Hospital on Nov. 20, 1939, of healthy parents, after a normal pregnancy and labor. Respiration was spontaneous. She was examined

From the Babies Hospital and the Departments of Pediatrics and Pathology, Columbia University College of Physicians and Surgeons.

1. van Creveld, S.: Glycogen Disease, Medicine **18**:1, 1939.

shortly after birth, and no abnormalities were noted. Besides breast milk, she received about 75 cc. of 5 per cent solution of sucrose on each of the first two days of life.

Course.—By the third day she had lost 300 Gm. from a birth weight of 3,620 Gm. She was slightly jaundiced, and her respirations were deep and labored. Because of dehydration she was given a clysis of 60 cc. of Ringer's solution. By evening she was in collapse, her respiration was more labored, there was an odor of acetone on her breath and her liver extended below the iliac crest on the right. Physical examination revealed no other abnormal signs. At this time the urine showed no sugar, but there was a positive reaction (4 plus) to tests for acetone and diacetic acid. The value for blood sugar was 15 mg. per hundred cubic centimeters, and the carbon dioxide–combining power of the blood was 32 volumes per cent. A blood count gave a value for hemoglobin of 17.2 Gm. per hundred cubic centimeters; the red cells numbered 4,960,000, and the leukocytes, 19,600, of which 80 per cent were polymorphonuclear leukocytes, 16 per cent small lymphocytes, 1 per cent myelocytes and 3 per cent monocytes; there was 1 nucleated red cell per hundred leukocytes.

For the next three days the patient was very ill. Most of the time she was stuporous and would take little by mouth, and her breathing was deep and labored. The carbon dioxide–combining power of the blood was continuously low, and acetone was present in all samples of urine. Her fluid and caloric intake was kept up by giving a solution of dextrose by gavage and solutions of dextrose and sodium lactate intravenously. The administration of sodium lactate apparently helped the patient less than did the solution of dextrose alone.

On the fifth day the infant took some breast milk and solution of dextrose by mouth. From this time on she began to gain weight and to act more normally, but she still had periods of hyperpnea. In the next two months she gained 1,200 Gm. When she was just over 2 months old an infection of the respiratory tract developed; after two days she became rapidly worse and died in acidosis.

Laboratory Data.—The results of chemical examinations on the blood are given in the table. The fasting blood sugar was always low, sometimes extremely low. The carbon dioxide–combining power of the blood was lower than normal most of the time, even while the patient was taking adequate amounts of food. The level of nonprotein nitrogen was high at first, fell to normal while she was doing well but rose before death. The level of cholesterol was somewhat high after the first two weeks. The values for calcium, inorganic phosphorus and phosphatase were within normal limits. The levels of bilirubin were characteristic of physiologic jaundice.

The specific gravity of the urine varied from 1.010 to 1.023. The urine always contained a trace of albumin. Sugar was present in many of the specimens obtained early, while the patient was receiving a considerable amount of dextrose intravenously. Later it was absent. Acetone and diacetic acid were present in large amounts in the specimens obtained during the first few days but not later, when the patient began to take adequate amounts of food. Unfortunately, only two specimens were examined for acetone during the two months that the patient was doing well.

Investigations on Blood Sugar.—As soon as the infant began to gain weight and to act normally, tests with epinephrine were done. The administration of neither 0.1 nor 0.2 mg. caused any rise in the level of blood sugar (fig. 1). Since the patient was receiving adequate amounts of food when these tests were done, we had to conclude that the liver was unable to change glycogen to dextrose.

Tolerance curves were determined after the ingestion of each of the three monosaccharides, dextrose, levulose and galactose. One and seventy-five hundredths grams of the sugar was fed for each kilogram of body weight. When dextrose was fed, the level of blood sugar rose much higher and stayed up longer than is usual. After dextrose was given intravenously it took an abnormally long time for the level of blood sugar to return to normal (fig. 2).

When levulose was fed, the level of blood sugar did not rise at all; in fact, it fell gradually (fig. 3).

Results of Examinations on the Blood

	Whole Blood, Mg. per 100 Cc.			Serum, Mg. per 100 Cc.							
Age, Days	Nonprotein Nitrogen	Sugar, Fasting	Plasma, Volumes per Cent; Carbon Dioxide-Combining Power	Chlorides as Sodium Chloride	Calcium	Inorganic Phosphorus	Cholesterol	Bilirubin	van den Bergh Reaction	Phosphatase, Bodansky Units
3	70	16	36	...	....	...	.....	10.2	.....	...
4	58	49	29	...	....	...	Total 114 Free 76 Combined 38 Ratio 0.5	11.6 Direct 0.7 Indirect 10.9	.....	...
5	..	56	..	...	....	...	.....	.....	.....	
6	..	..	..	597	11.6	3.4	.....	12.6	.....	7.9
7	34	25	54	573	....	...	.....	.....	.....	...
10	..	..	35	...	....	...	.....	.....	.....	...
14	..	53	36	...	12.0	7.2	Total 300 Free 168 Combined 192 Ratio 1.1	2.0	.....	9.2
21	..	13	28 20	621 ...	....	6.9 ...	Total 207 Free 93 Combined 114 Ratio 1.2	Direct 0.6	Direct + Indirect +	
23	..	..	38 34							
44	..	20	34							
50	..	..	28							
75	78	22	14							

The same was true when galactose was used. One day the level of fasting blood sugar was so low that it could not be read with certainty. Nor did it rise after the ingestion of galactose (fig. 4).

After an ordinary feeding of evaporated milk and sucrose, the blood sugar rose to an abnormally high level and stayed up for an excessively long time (fig. 5).

Autopsy.—Autopsy was performed three and a half hours after death.

Gross Examination: The body was that of a well developed, well nourished 3 month old infant, showing a normal distribution of subcutaneous fat. It was 58.5 cm. long and weighed 4.8 Kg. The chief abnormalities on external examination were the protuberance of the abdomen and the flaring of the costal margins, which gave a costal angle of approximately 130 degrees. Opening of the peritoneal

cavity revealed that the abdominal enlargement was due to extreme enlargement of the liver. The margin of the liver lay 8.5 cm. below the xiphoid process, 9.5 cm. below the costal margin in the right midclavicular line and 2 cm. below the right

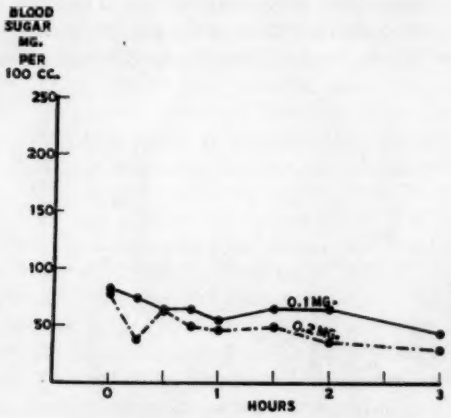

Fig. 1.—Blood sugar curves, showing the lack of rise after the subcutaneous injection of epinephrine.

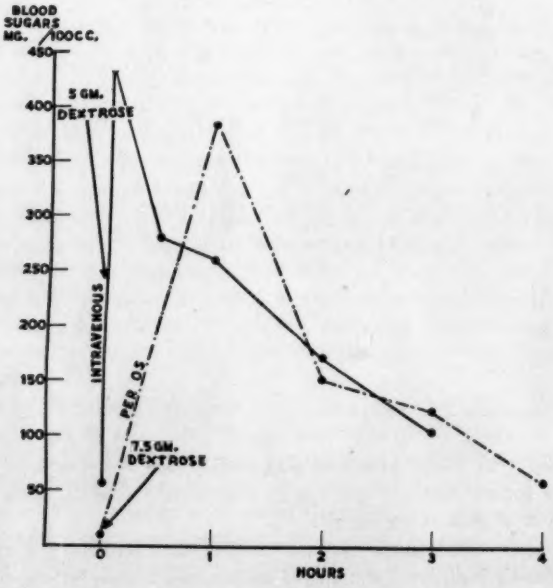

Fig. 2.—Results of oral and intravenous dextrose tolerance tests, showing the abnormal height and prolongation of the blood sugar curves.

iliac crest. The diaphragm lay at the level of the fourth interspace on the right and of the fifth on the left. The intestines were compressed into the left lower quadrant of the abdomen by the enormous liver. The peritoneal surfaces were

normal. The pleural and pericardial cavities were normal. The heart lay in the transverse position because of the abdominal distention.

Heart. The heart weighed 25 Gm. (normal, 23 Gm.) and appeared normal. The coronary arteries were somewhat tortuous and prominent. The foramen ovale was patent, there being a narrow slit along the anterior margin. The myocardium was firm and pale red and of normal thickness. The aorta was normal.

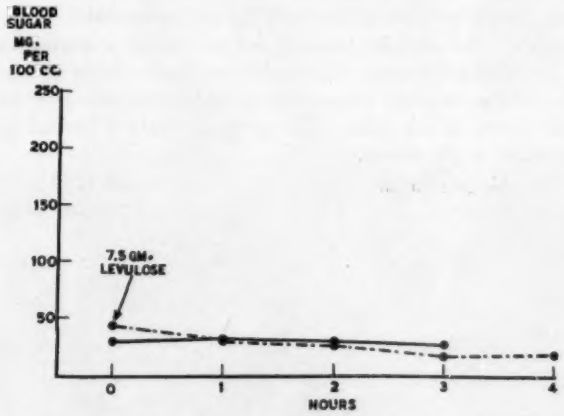

Fig. 3.—Results of two levulose tolerance tests, showing the lack of rise of the blood sugar curves after the ingestion of levulose.

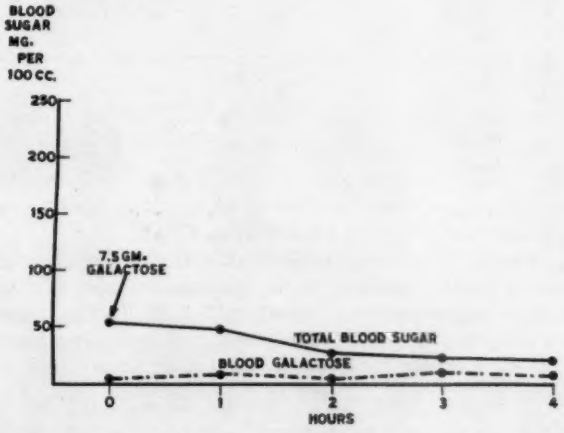

Fig. 4.—Results of galactose tolerance test, showing the lack of rise of the blood sugar curve after the ingestion of galactose.

Lungs. The right lung weighed 57 Gm. and the left 59 Gm. They showed no abnormalities other than edema, as indicated by dilated pleural lymphatics, a moist, pale red cut surface and the presence of foamy fluid in the bronchi.

Liver. The liver weighed 770 Gm. (normal, 140 Gm.) and measured 18 by 13 by 5.5 cm. The contours were somewhat altered by pressure on adjacent struc-

tures, especially the costal margin. The margins were sharper than one would expect with this degree of enlargement. The surface was smooth and pale buff. The lobular pattern was marked by faintly pinkish lines. The liver cut easily, and the cut surface bulged slightly above the level of the capsule and the vessels. The surface was moist, somewhat greasy and pale buff, with the lobular pattern marked faintly in pink.

Kidneys. The right kidney weighed 32 Gm. (normal, 20 Gm.) and measured 6 by 3.5 by 2 cm. The left kidney weighed 26 Gm. and measured 5.7 by 3.3 by 2 cm. They were similar. The capsule stripped easily, leaving a surface which was smooth except for fetal lobulations. The color was pale salmon pink, with many minute red dots. The cut surface was normal except for an unusually thick cortex, which measured 5 mm. in thickness. The pyramids were a normal pale red, in contrast to the pallor of the cortex.

Other Organs. No significant abnormalities were found in the spleen, gallbladder, pancreas, adrenals, pelvic organs, gastrointestinal tract, thyroid gland,

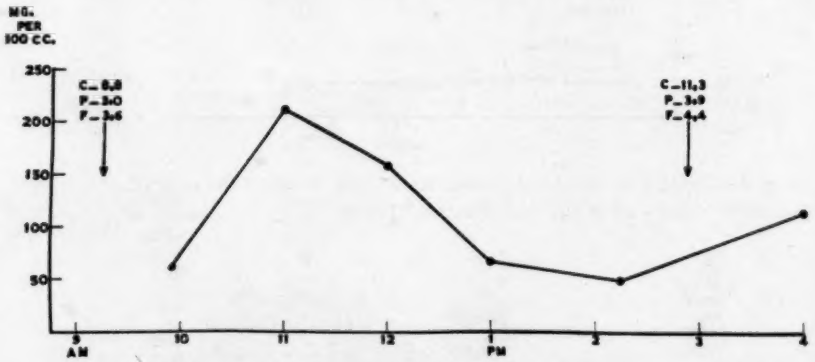

Fig. 5.—Blood sugar curve, showing the unusual height and prolongation of the curve after the ingestion of 110 cc. of cow's milk with 6 Gm. of sucrose.

thymus, striate muscle, bones, pituitary gland or brain. Both middle ears contained mucopurulent exudate, but both mastoids appeared normal.

Bacteriologic Report: Cultures of material from the ears showed: many pneumococci, type XIV; smaller numbers of Staphylococcus aureus nonhaemolyticus; Staphylococcus albus nonhaemolyticus; diphtheroids, and Bacillus proteus.

Microscopic Examination: Heart. The pericardium and myocardium appeared normal. Near the endocardium there were a few muscle fibers which showed pale areas near the poles of the nuclei. A few of the endocardial cells were somewhat prominent.

Throughout the sections prepared with Best's glycogen stain there were rare fibers which contained a small amount of glycogen at the poles of the nuclei. Beneath the endocardium there were a number of fibers which took the stain more diffusely but had the main deposits near the nuclei. Occasional hypertrophied endocardial cells took the stain.

The muscle fibers in the sections stained with scarlet red contained no fat.

Lung. The alveolar walls were somewhat thickened, and the capillaries were engorged. A few alveoli contained edema fluid and occasional red cells. The bronchi appeared normal.

In the sections prepared with Best's glycogen stain every cell in the cartilage of the bronchi took the stain. Occasional red cells also stained. The other tissues did not.

Liver. The lobular pattern was normal, with normal portal areas and small central veins. The liver cells were large and appeared packed together, compressing the sinuses. Each cell contained a single large fat vacuole, on one side of which was a moderate amount of pale, empty-looking cytoplasm, containing a normal nucleus. In the central areas the fat vacuoles tended to be somewhat larger and the cytoplasm scanty, so that the nucleus was flattened. Glisson's capsule was thin. Examination of frozen sections with a polarizing microscope revealed the presence of large amounts of doubly refractile material within the fat droplets.

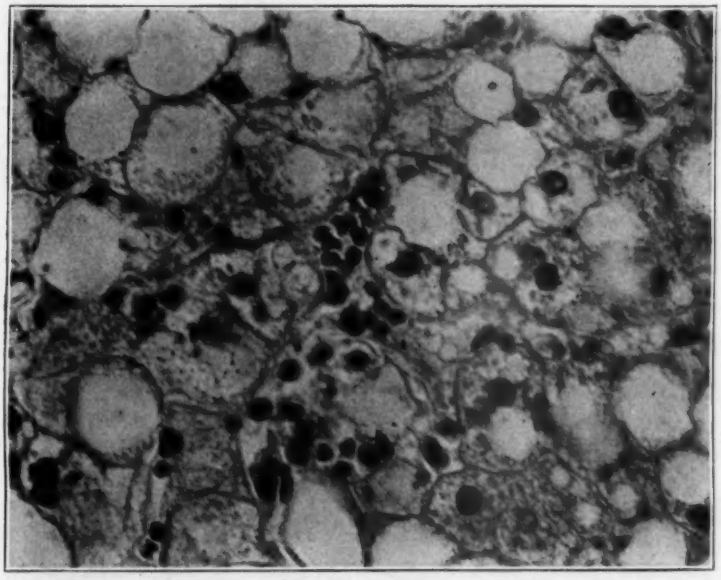

Fig. 6.—Section of the liver, showing an area in which the fat vacuoles were smallest and the glycogen most abundant (hematoxylin-eosin stain).

Examination of the sections stained with scarlet red confirmed the presence of large fat droplets in the liver cells.

In the sections prepared with Best's glycogen stain glycogen granules occupied nearly all of the cytoplasm not replaced by fat. The glycogen was more abundant in the cells near the portal areas. The glycogen appeared to have diffused and to have been somewhat smeared, for there were granules in the portal spaces and in the capsule, not in relation to cells. Some of the red cells in the vessels took the stain. The bile ducts contained no glycogen.

Kidney. The cortex appeared wide and extremely pale. The glomeruli were normal and stood out as dark nodules against the pallor of the remaining cortex. The proximal and the distal convoluted tubules were moderately dilated. The epithelial cells were several times the normal size and appeared as large spaces, with a normal nucleus near the basement membrane. They contained no vacuoles,

but there was little stained material in the cytoplasm. The cells of Henle's loop and of the collecting tubules appeared normal. The small vessels of the pyramids appeared congested, and there were a few petechial hemorrhages.

In one or two areas of the sections stained with scarlet red there were a few fine fat droplets at the base of the epithelial cells of the distal convoluted tubules and in portions of Henle's loop. Part of this fat was doubly refractile.

In the sections prepared with Best's glycogen stain there were large amounts of glycogen in practically every cell of both the proximal and the distal convoluted tubules, and all the tubular lumens were packed with it. It appeared as irregular granules, varying in size up to the approximate dimensions of the epithelial nuclei. Small amounts of glycogen were present in the capsular spaces, but little or none was present in the glomeruli themselves. The collecting tubules were also free

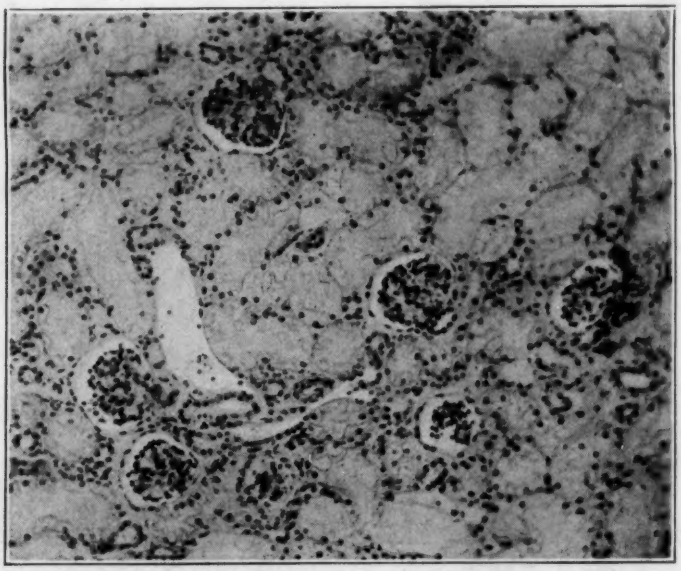

Fig. 7.—Section of the kidney, showing the large tubular epithelial cells from which glycogen had been dissolved. The glomeruli were normal (hematoxylin-eosin stain).

from it. There appeared to have been some diffusion and perhaps a little mechanical smearing of the glycogen, for granules were found in the connective tissue near large deposits but only occasionally in connective tissue in the pelvis at a distance from them. This may be the explanation of the difficulty often encountered in perceiving the exact location of glycogen in the cells.

Tongue. In the sections prepared with Best's glycogen stain the muscle fibers appeared normal and contained no glycogen. Many of the mucous glands, however, contained large amounts of it. The glycogen appeared in some cells or tubules and not in adjacent ones. The superficial epithelium took a diffuse red stain.

Thymus. This gland appeared normal.

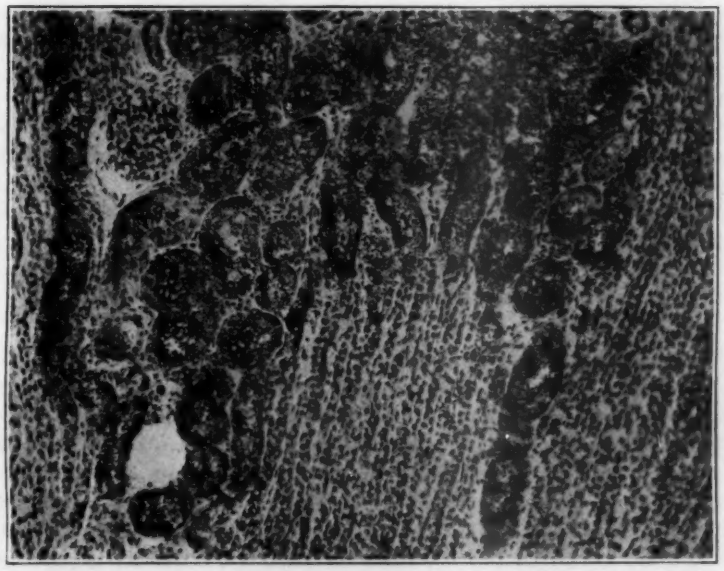

Fig. 8.—Section of the kidney. The glycogen was confined to the cells and the lumens of the convoluted tubules (Best's glycogen stain).

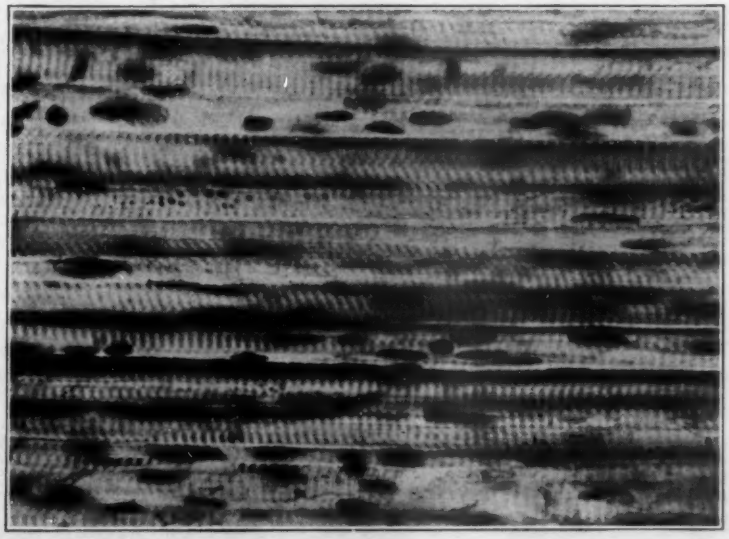

Fig. 9.—Section of striate muscle, showing glycogen along the transverse striations and in the granules in the centers of some fibers (Best's glycogen stain).

In the sections prepared with Best's glycogen stain there was a pink tinge to some of Hassall's corpuscles.

Psoas Muscle. The muscle fibers were somewhat uneven in staining quality. The striations were distinct. The nuclei were normal.

In the sections prepared with Best's glycogen stain there was glycogen in a large number of muscle fibers. The amount was small, and the glycogen deposits appeared to follow the pattern of the cross striations. In a few fibers there were large granules which occupied the central portion.

Diaphragm. The muscle fibers appeared normal except for unusually distinct striations.

In the sections prepared with Best's glycogen stain occasional fibers showed a small amount of glycogen marking the cross striations. There was less glycogen than in the psoas muscle.

Brain and Spinal Cord. The cortex and the meninges appeared normal. There was some edema of the perivascular spaces.

In the sections prepared with Best's glycogen stain many of the glia cells had a diffuse pink tinge, but none contained definite glycogen granules. Sections through the basal ganglions, cerebellum, corpora quadrigemina, pons and medulla appeared similar. The anterior horn cells of the spinal cord stained a diffuse pink.

Other Organs. No significant changes and no glycogen were found in the spleen, pancreas, adrenal, ovary, small intestine, colon, mesentery, thyroid, parathyroid, skin, rib, temporal bone or pituitary gland.

The Anatomic Diagnosis.—The diagnosis was glycogen storage disease (von Gierke's disease); glycogen deposits in the liver, kidney, heart, tongue, striate muscle and bronchial cartilage; fatty liver; edema of the lungs, and otitis media, bilateral.

CHEMICAL AND ENZYME STUDIES

1. *Glycogen Content of Tissues.*—Weighed portions of various organs were minced and covered with approximately twice their volume of 50 per cent solution of potassium hydroxide at the time of autopsy. They were then placed in the refrigerator. Two days later they were boiled until the tissue was dissolved; the glycogen was precipitated with alcohol and hydrolyzed with 0.6 normal hydrochloric acid. The dextrose was then measured by the Benedict method. The glycogen content in terms of fresh weight was as follows: liver, 4.10 per cent; kidneys, 3.65 per cent; heart, 0.16 per cent; diaphragm, 0.06 per cent; psoas muscle, 0.43 per cent, and tongue, 0.09 per cent. Control figures given by van Creveld are: liver, 0.103 per cent; kidney, 0.062 per cent; heart, 0.07 per cent, and muscle, 0.011 per cent. It will be seen that there is a significant increase in the glycogen content of the liver, kidneys and psoas muscle in our case.

2. *Autolysis Experiments.*—Portions of the liver and the kidney were kept in the ice box, without preservative, for nine days and were then subjected to the procedure previously described. It was known that some material was lost in the handling of the liver tissue. The figure for the liver tissue was 3.06 per cent (original, 4.10 per cent), and for the kidney, 3.92 per cent (original, 3.65 per cent). The discrepancy in the latter figures is within the limits of analytic error.

3. *Fat Content of Liver.*—Six and thirty-seven hundredths grams of tissue was ground with sand, mixed with an equal volume of anhydrous sodium sulfate and

subjected to continuous extraction with ether for eight hours in an apparatus functioning on the plan of a Soxhlet flask. The ether was evaporated off and the material weighed.

Analysis of the liver gave the following results:

	Wet Weight, Per Cent	Dry Weight, Per Cent
Glycogen	4.1	8.88
Fat	31.1	64.3
Other solids	13.1	26.8
Water	51.1	....

The low water content is unusual but is readily explained by the high fat content. It bears a normal relation to the amount of residual solids.

4. *Amylolytic Activity of the Liver.*—The substrate used was a sterile 5 per cent starch solution buffered to a p_H of 5.6 with sodium acetate. A portion of the liver was sliced thin and placed in an approximately equal volume of 50 per cent glycerin at the time of autopsy. It was kept on ice for four days, finely ground with sand and strained through coarse gauze. One cubic centimeter of this material was added to 5 cc. of the starch substrate. As a control a similar amount of the same material was placed in boiling water for twenty minutes to destroy the enzyme and cooled, and to it was added 5 cc. of substrate. The experiment was run in duplicate. The tubes were incubated at 37 C. for twenty hours. No trace of dextrose was found in any of the tubes by Benedict's method.

Viscosimetric Method: Four days after death 1 cc. of the extract described was added to 10 cc. of the starch substrate; 5 cc. of the mixture was placed in each of two Ostwald viscosimeters in a water bath kept at 37.5 C. The viscosity was measured at intervals, but no change was found.

5. *Glycogenolytic Activity of the Liver.*—The liver mash was prepared as described previously and was kept on ice until glycogen and control liver mash was available. The glycogen was obtained from three sources: (1) from the patient's own liver, by precipitation, washing and drying; (2) from oyster, and (3) from the liver of a patient with diabetes, with large deposits of glycogen. The last two preparations were supplied by Dr. James J. McBride. Each glycogen preparation was made up in sterile aqueous solution containing 32 mg. per cubic centimeter. Two buffers were used, each made up in such a way that the concentration of the digestion mixture was fifteenth molar: (1) a mixture of sodium phosphate and potassium phosphate (Na_2HPO_4—KH_2PO_4), at a p_H of 7.0, and (2) a mixture of sodium acetate and acetic acid (CH_3COONa—CH_3COOH), at a p_H of 5.6. The digestion mixture was composed of 1 cc. of glycerinated liver mash, 2 cc. of glycogen solution and 2 cc. of buffer, and it was incubated for twenty hours at 37 C. At the end of the period the dextrose was measured, and from this figure the percentage of glycogen converted into dextrose was calculated. The remaining glycogen was not measured, and additional glycogen may have been converted into carbon dioxide and water. Control material was obtained from the livers of 2 patients on whom autopsy was performed: (1) a 62 year old man who died of carcinoma of the prostate, and (2) a 75 year old man who died of generalized tuberculosis. Unfortunately, no control material was available from a subject of an age similar to the patient's. The experiment was first carried out with material from 1 control, but since the interval between autopsy and the experi-

ment was less for the control, part of the experiment was repeated a week later, and material from a second control was added. The results were as follows:

Liver Mash	Days After Death	Source of Glycogen	Buffer	Glycogen Converted to Dextrose, Per Cent
S. L.....	17	S. L.	Phosphate	0
Control 1.....	8	S. L.	Phosphate	17.4
S. L.....	17	Oyster	Phosphate	0
Control 1.....	8	Oyster	Phosphate	19.0
S. L.....	17	Patient with Diabetes	Phosphate	0
Control 1.....	8	Patient with Diabetes	Phosphate	19.0
S. L.....	17	S. L.	Acetate	0
Control 1.....	8	S. L.	Acetate	37.07
Control 1.....	15	S. L.	Acetate	34.8
Control 2.....	13	S. L.	Acetate	9.0

Conclusions: 1. Glycogen from the liver of the patient was split by mash prepared from the livers of 2 other patients, when either phosphate or acetate buffer was used, in about the same degree as was glycogen from two other sources. 2. Mash prepared from the patient's liver was unable to split glycogen from three sources when either a phosphate or an acetate buffer was used, while mash made from the livers of 2 controls was able to do so. It is apparent from these results that the defect in glycogenolysis in our case lies not in the character of the glycogen but in the enzyme system of the liver.

COMMENT ON THE CASE

The complete lack of response to epinephrine in adequate dosage could be due to any of three conditions: first, an abnormality in the glycogen of the liver; second, a small store of glycogen in the liver or, third, complete or severe impairment of the enzyme system of the liver that converts glycogen to dextrose. Abnormality in the liver glycogen of the patient seemed unlikely because the glycogen was readily broken down by mash made from the livers of 2 other patients. These results agree with those of all investigators except Kimmelstiel.[2] The second of these conditions we have reason to believe was not the cause, because the patient had received an adequate supply

2. (*a*) von Gierke, E.: Hepato-Nephromegalia glycogenica (Glycogenspeicherkrankheit) der Leber und der Nieren, Beitr. z. path. Anat. u. z. allg. Path. **82**:497, 1929. (*b*) Schönheimer, R.: Ueber eine eigenartige Störung des Kohlehydratstoffwechsels, Ztschr. f. physiol. Chem. **182**:148, 1929. (*c*) Unshelm, E.: Die Glykogenkrankheit (zugleich ein Beitrag zur Frage des hepatogenen Infantilismus), Jahrb. f. Kinderh. **137**:257, 1932. (*d*) Kimmelstiel, P.: Ueber Glykogenose, Beitr. z. path. Anat. u. z. allg. Path. **91**:1, 1933. (*e*) Faber, V.: Ueber die Glykogenkrankheit (Hepatonephromegalia glycogenica), Frankfurt. Ztschr. f. Path. **47**:443, 1935. (*f*) Faber, V., and Vendég, V.: Vergleichende Untersuchungen am Leberglykogen eines glykogenkranken Säuglings und an jenem normaler Tiere, Ztschr. f. d. ges. exper. Med. **97**:86, 1935. (*g*) Karlstrom, F.: Glycogenosis, Acta pædiat. **20**:497, 1938.

of carbohydrate previous to the tests and because the amount of glycogen found in the liver at autopsy was large. Therefore we believe that the third condition, a defect in the enzyme system of the liver, was the reason for the lack of response to epinephrine and for the large accumulation of glycogen in the liver. The result of the experiments in vitro with liver tissue from the patient led to the same conclusion.

The high, prolonged blood sugar curves after the ingestion and the intravenous administration of dextrose suggested that the ability of the liver to convert dextrose to glycogen was seriously impaired. High prolonged blood sugar curves may be due to a low carbohydrate diet,[3] but this patient had received large amounts of carbohydrate previous to the test. Furthermore, after the patient was gaining weight regularly the blood sugar curve after the ingestion of the usual feeding of milk and sucrose was high and prolonged. Therefore, we think that the ability of the liver in this case to convert dextrose to glycogen, as well as its ability to convert glycogen to dextrose, was seriously impaired. If this reaction is reversible in the body, any defect in the enzyme system might affect the reaction going in either direction.

The extremely flat blood sugar curves after the ingestion of levulose and galactose could be due to lack of absorption of the sugar from the alimentary canal, but we have no evidence to support this. There is evidence that dextrose was absorbed. Thus we are forced to conclude that the first-mentioned sugars were absorbed normally into the portal blood and removed completely from the blood on their first passage through the liver. This being so, the glycogen in this liver must have been largely formed from levulose and galactose and other precursors of glycogen except dextrose.

Thus, this was a liver that could and did make glycogen from levulose and galactose and probably from other precursors of glycogen but was deficient in its ability to make glycogen from dextrose and was unable to change glycogen back to dextrose, no matter what the source of the glycogen. This disability of the liver, we believe, was due to some defect in its dextrose to glycogen and glycogen to dextrose enzyme system.

In an effort to identify more exactly the enzyme reaction which was at fault in this case, we studied the outline of the steps involved in the transformation of dextrose to glycogen and glycogen to dextrose in the liver as recently presented by Cori and his associates.[4] There

3. Conn, J. W.: Interpretation of the Glucose Tolerance Test: The Necessity of a Standard Preparatory Diet, Am. J. M. Sc. **199**:155, 1940.

4. (*a*) Cori, G. T.; Cori, C. F., and Schmidt, G.: The Role of Glucose-1-Phosphate in the Formation of Blood-Sugar and the Synthesis of Glycogen in the Liver, J. Biol. Chem. **129**:629, 1939. (*b*) Cori, C. F.: Symposium on Carbohydrate Metabolism: Glycogen Breakdown and Synthesis in Animal Tissues, Endocrinology **26**:285, 1940.

appear to be two possibilities: (1) There may be a defect somewhere in the reversible reactions involved in the steps between glycogen and dextrose 1-phosphate or dextrose 6-phosphate, or (2) the defect may lie in the reversible reaction: dextrose monophosphate ⇄ dextrose.

1. The hypothesis that the defect lies in the glycogen ⇆ dextrose monophosphate reaction explains the absence of the glycogen ⇆ dextrose reaction. It also suggests an explanation of the ketosis, since the liver would then be unable to utilize glycogen for its own carbohydrate needs and in depending on fat as a source of energy would produce large amounts of the products of fat metabolism. This hypothesis presupposes that both galactose and levulose can be transformed into glycogen by a mechanism entirely different from that required for dextrose, since both galactose and levulose were used to form glycogen in our case. Since the exact mode of transformation of these two sugars to glycogen has not been clearly established, the question must be left open at present.

2. If the defect lies in the dextrose monophosphate ⇄ dextrose reaction, the absence of the dextrose ⇄ glycogen reaction could be explained without presupposing that levulose forms glycogen by a mechanism different from that of dextrose, as galactose must do. On the other hand, according to Cori's outline, the breakdown of glycogen to lactic acid or carbon dioxide and water should be uninterrupted. If this is true, the liver should be able to utilize glycogen for its own needs. Under these conditions the ketosis cannot be explained as the result of the burning of fat for the use of the liver itself. The only explanation that occurs to us is that some stimulus originating outside the liver, such as the extremely low blood sugar, demanded that the liver free some source of energy; the liver was unable to free dextrose and responded with the breakdown of fat. This explanation is tentative, since the function of ketones in fat metabolism is not yet clear. One piece of experimental evidence in favor of this second hypothesis was presented by Thannhauser and his associates,[5] who found a low level of alkaline phosphatase in the liver in 3 cases of von Gierke's disease. The reaction dextrose → dextrose monophosphate requires some such enzyme.

The hypothesis that there is a defect somewhere in the glycogen ⇄ dextrose enzyme system appears to explain most of the features of the case. It explains the hypoglycemia on fasting and the hyperglycemia on the ingestion of dextrose. The presence of considerable glycogen

5. Thannhauser, S. J.; Sorkin, S. Z., and Boncoddo, N. F.: The Amylolytic and Phosphatase Activity of Liver Tissue in von Gierke's Disease, J. Clin. Investigation **19**:681, 1940.

in the other organs may be the result of the hyperglycemia that followed every meal and the resulting hypersecretion of insulin. We do not know of any experimental evidence as to whether these organs in cases of von Gierke's disease are or are not able to break down glycogen, except the fact that the glycogen does not disappear as rapidly from the tissues after death in such cases as from normal tissues. Perhaps the fact that many times the normal amount of glycogen is present in the tissues slows up its disappearance. Perhaps there is sufficient insulin present to accomplish this. There is no experimental evidence to support either of these theories. We do know that our patient was able to utilize carbohydrate in most of the tissues, because after the first week she ate normal amounts and excreted almost no sugar and few ketones, and at death all the glycogen stores would nowhere near account for all the carbohydrate ingested.

In the light of present knowledge of carbohydrate metabolism of the liver, the hypothesis which best explains the features of this case appears to be the presence of a defect in one of the enzyme reactions necessary for the transformation of glycogen to dextrose and dextrose to glycogen in the liver. The exact step in the chain of reactions which is at fault cannot be determined by means of the data at hand. Two possibilities are discussed, in the hope that further experimental evidence will be accumulated as appropriate cases present themselves.

REVIEW OF THE LITERATURE

The possibility that the cases reported under the diagnosis of glycogen storage disease are not in fact uniform in respect to the etiologic factors involved has already been suggested in this paper. In the rather large number of reported cases, comparable studies have given widely different results; the injection of epinephrine has produced no rise in blood sugar in some cases and a moderate to high rise in others; the liver has failed to autolyze its glycogen in some cases, and in others the breakdown of glycogen has proceeded at a normal rate; the site and amount of glycogen deposits have varied; in the few reported cases in which there were studies of enzyme activity in vitro results were discordant. In order to clarify the subject, all cases in the literature reported as examples of glycogen storage disease have been collected. To this group have been added a few cases closely resembling them but not so diagnosed. The clinical, laboratory and postmortem observations have been analyzed and, so far as possible, classified on the basis of the functional defects. In view of the meager knowledge of normal carbohydrate metabolism, the still vaguer concepts of the pathologic changes and the incomplete studies in most of the cases, this classification is to be regarded as tentative.

The criteria used for the diagnosis in the reported cases have been various. Three errors have recurred: 1. The presence of glycogen within the liver cells of tissue removed at operation and fixed at once does not establish the diagnosis of glycogen disease. Glycogen is present in normal liver but disappears rapidly after death. It is the absence of glycogenolysis which is abnormal in cases of von Gierke's disease, not the presence of glycogen.

2. Hepatomegaly and delay in growth are found in several diseases of childhood in addition to glycogen storage disease. Several of the cases included in the present analysis appear to have been cases of cirrhosis of the liver, in which destruction of liver tissue had altered the capacity of the liver to metabolize carbohydrates. Cases of cirrhosis of the liver in childhood present many of the same features found in cases of von Gierke's disease;[6] the child may show deficient growth and development; there is often moderate hypoglycemia,[7] and there may be prolonged galactose and dextrose tolerance curves. Information as to the response to epinephrine has not been noted, but some decrease in the degree of response is probable on theoretic grounds and on the basis of experimental evidence.[7a] Biopsy material from the normal or the cirrhotic liver, if fixed in alcohol at once, will usually show a deposit of glycogen within the cells. Such a procedure might well lead to an erroneous diagnosis of von Gierke's disease. This seems to have been the explanation of several cases included in the series, for example, those of Lindsay, Ross and Wigglesworth[8] and of Chrometzka and Brunssen.[9] In the latter case there was no acetonuria, and the liver tissue split glycogen in vitro. Cirrhosis of the liver was also demonstrated in the case reported by Kimmelstiel[2d] and Unshelm,[2c] in case 4 of Debré and Semelaigne[10] and in case 2 of Gold-

6. (*a*) Amberg, S.: Diseases of the Liver and Biliary Tract, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 11, pp. 48-50. (*b*) Harnapp, G. O.: Zur Klinik der Hepatomegalien mit Kohlehydratstoffwechsel-Störungen: I. Glykogenspeicherungskrankheit, Monatschr. f. Kinderh. **66**:169, 1936; II. Fettleber und Cirrhose, ibid. **66**:184, 1936; III. Differential-Diagnose und Pathogenese der Glykogenspeicherungskrankheit, ibid. **66**:194, 1936. (*c*) Linneweh, F.: Zur Differentialdiagnose kindlicher Lebertumoren, ibid. **67**:422, 1936.

7. (*a*) Mann, F. C.: Hepatic Function in Relation to Hepatic Pathology: Experimental Observations, Ann. Int. Med. **8**:432, 1934. (*b*) Amberg.[6a]

8. Lindsay, L. M.; Ross, A., and Wigglesworth, F. W.: Von Gierke's Glycogen Disease, Ann. Int. Med. **9**:274, 1935.

9. Chrometzka, F., and Brunssen, H.: Ferment-chemische Untersuchungen über die Glykogenspeicherkrankheit (von Gierke), Ztschr. f. klin. Med. **136**:122, 1939.

10. Debré, R., and Semelaigne, G.: Stéatose hypertrophique du foie chez un nourrisson, Presse méd. **38**:1742, 1930.

man.[11] There is no proof that glycogen storage disease leads to cirrhosis of the liver, and in most of the best authenticated cases cirrhosis was not observed. On the other hand, the presence of cirrhosis does not, so far as we know, rule out the possibility of concomitant glycogen disease, if the other features of the case give evidence adequate for the diagnosis. It seems, however, that proved cirrhosis of the liver should lead to skepticism of the diagnosis of glycogen storage disease, unless there is convincing evidence of the latter.

3. Until recently it has been supposed that in all cases abnormal deposition of glycogen in the liver has been based on a defect of the glycogen or of "glycogenase," a single enzyme presumed to be responsible for the splitting of glycogen. No abnormalities in the glycogen have been demonstrated, and it has been shown by several workers[12] that glycogen from the liver of patients with von Gierke's disease is split in the usual manner by the liver from other patients. The work of Kimmelstiel[2d] alone stands in contradiction. The concept of a single enzyme, "glycogenase," must be discarded in view of the recent demonstration that the carbohydrate metabolism of the liver is a highly complex process involving a series of reactions effected by a number of enzymes and coenzymes.[13] It is possible that the absence or abnormality of any one of these reactions might produce a block in the system having for its morphologic result an abnormal deposition of glycogen in the liver. Confirmation of this view may be found in the recent paper by Thannhauser, Sorkin and Boncoddo,[5] who demonstrated a low alkaline phosphatase activity but a normal amylase activity by the maltose method in 3 cases of von Gierke's disease. It is therefore necessary to consider the possibility that even among those cases in which glycogen is stored because of a primary defect in liver metabolism there may be some variations in the fundamental functional abnormality.

There remains the question of terminology. For the purposes of this paper "glycogen storage disease" is used to include all cases in which there was an abnormally large amount of glycogen in one or more organs; "glycogen storage disease of the liver" is used to include those cases in which the chief deposit of glycogen was in the liver; "von Gierke's disease" is employed only in those cases in which the excess deposit of glycogen in the liver appeared to result from the inability of the liver to break down glycogen (this classification may

11. Goldman, F.: Etudes sur la maladie glycogénique, Rev. franç. de pédiat. **14**:494, 1938.

12. Schönheimer.[2b] Kimmelstiel.[2d] Faber and Vendég.[2f] Present report.

13. Ostern, P.; Herbert, D., and Holmes, E.: Formation and Breakdown of Glycogen in the Liver, Biochem. J. **33**:1858, 1939. Cori, Cori and Schmidt.[4a] Cori.[4b]

prove to include several disease entities), and "glycogen storage disease of the heart" includes those cases in which the chief deposit of glycogen was in the heart. The plan of classification is outlined as follows:

Division I. Cases in which the main deposit of glycogen was in the liver (glycogen storage disease of the liver).

Group 1. Cases in which it appears probable that the primary defect was a complete or a partial inability of the liver to transform glycogen into dextrose and possibly dextrose into glycogen (von Gierke's disease; 34 cases, including the present one).

Subgroup A. Cases in which the rise in blood sugar after the administration of epinephrine was less than 10 mg. per hundred cubic centimeters (15 cases, including the one here reported.)

Subgroup B. Cases in which the rise in blood sugar after the administration of epinephrine was between 10 and 40 mg. per hundred cubic centimeters (11 cases).

Subgroup C. Cases in which no blood sugar curves after the administration of epinephrine are reported but in which postmortem observations have shown that the liver failed to break down its glycogen (2 cases).

Subgroup D. Cases in which no blood sugar curves after the administration of epinephrine or postmortem enzyme studies are reported but in which postmortem examination revealed a gross excess of glycogen in the liver and the kidney (6 cases).

Group 2. Cases of chronic galactosuria with hepatomegaly, in which the liver appeared unable to metabolize galactose normally.

Group 3. Cases of fructosuria, in which the liver appeared to be unable to form glycogen from levulose but in which there was usually no hepatomegaly.

Group 4. Cases of abnormal regulation of insulin in the body, with glycogen deposited in the liver.

Subgroup A. Cases of hyperinsulinism resulting from tumor of the islands of Langerhans in which large amounts of dextrose had been given.

Subgroup B. Cases of diabetes mellitus in which large amounts of insulin and dextrose had been given.

Group 5. Cases not classifiable in the preceding groups, sometimes because of inadequate data.

Division II. Cases in which the main deposit of glycogen was in the muscles, including the heart muscle.

Group 1. Cases in which the heart contained massive, diffuse deposits (glycogen storage disease of the heart). Only those cases in which the glycogen was demonstrated by staining reaction or by chemical means are discussed (11 cases).

Group 2. Cases in which the striate muscle was chiefly affected (1 case).

DIVISION I: *Group 1.*—Subgroup A: In this subgroup there are 15 cases, including the one here reported.[14] The clinical picture is that usually described as classic von Gierke's disease, with hepatomegaly noted soon after birth or in infancy, a low fasting blood sugar, sensitivity to insulin, a prolonged and often biphasic dextrose tolerance curve and acetonuria. The tolerance curves for other sugars have various forms. In 2 of Schall's cases the galactose tolerance curve was described

14. (*a*) Snapper, I., and van Creveld, S.: Un cas d'hypoglycémie avec acétonémie chez un enfant, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1315, 1928. (*b*) Beumer, H., and Löschke, A.: Zum Stoffwechsel und zur Differentialdiagnose der Glykogenspeicherkrankheit, München. med. Wchnschr. **80**:377, 1933. (*c*) Beumer, H., and Loschke, A.: Zum Stoffwechsel bei der Glykogenspeicherungskrankheit, Klin. Wchnschr. **11**:1824, 1932. (*d*) Schall, L.: Drei Fälle von Glykogenspeicherkrankheit (Hepatomegalia glykogenetica von Gierke), München. med. Wchnschr. **79**:2078, 1932. (*e*) Warner, E. C.: A Case of Hepatomegaly Due to von Gierke's Disease, Lancet **1**:1070, 1933. (*f*) Warner, E. C.: Hepatomegaly of Unknown Origin (Probably von Gierke's Disease), Proc. Roy. Soc. Med. **26**:1006, 1933. (*g*) Biedermann, H., and Hertz, W.: Zur Glykogenspeicherkrankheit. Klinische Beobachtungen, Ztschr. f. Kinderh. **56**:170, 1934; (*h*) Die Verwertungsmöglichkeit genossenen Zuckers bei Glykogenspeicherkrankheit, Deutsches Arch. f. klin. Med. **176**:267, 1934; (*i*) Der Einfluss von Adrenalin und Insulin auf den Kohlehydratstoffwechsel bei Glykogenspeicherkrankheit, ibid. **176**: 272, 1934. (*j*) Anderson, P. M., and Vickery, D. G. R.: Von Gierke's Glycogen Accumulation Disease, M. J. Australia **1**:753, 1934. (*k*) Holmes à Court, A., and Bray, S. D.: Hepato-Nephro-Megalia Glycogenica (von Gierke), ibid. **1**: 755, 1934. (*l*) Krackower, C.: The Lipoid Factor in Glycogen Storage Disease, J. Pediat. **9**:728, 1936. (*m*) Erben, F., and Küster, F.: Glykogenspeicherkrankheit, Ztschr. f. Kinderh. **58**:178, 1936. (*n*) Hogg, P., and Sidbury, J. B.: A Case of von Gierke's Disease with Marked Lipemia, J. Pediat. **10**:798, 1937. (*o*) McKeon, J. A.: Von Gierke's Disease: A Case Report with Comment, Newcastle M. J. **17**:79, 1937. (*p*) Karlstrom.[2g]

as prolonged, though it was not reported on in detail. In our case the galactose tolerance curve was definitely flat. In these and in 2 other cases no sugar appeared in the urine after galactose was given. The levulose tolerance curve was described in 9 cases; again the results varied. In the present case the curve was flat, and in Warner's case the rise in blood sugar was slight, but in the other 7 there was a moderate to high rise in blood sugar. The level of blood glycogen was high in the 2 cases in which it was studied. The blood level of blood cholesterol varied from low to high. The fat tolerance curve was high in 1 case. Biopsies of the liver showed large deposits of glycogen in 3 cases. Autopsy reports have been given in only 2 cases of this subgroup, in both of which enlargement of the liver and the kidneys with an excess of glycogen was noted (Karlstrom [2g] and the present case). Karlstrom's figures for glycogen are as follows: liver, 19.2 per cent; kidney, 1.40 per cent; heart, 2.0 per cent, and skeletal muscle, 6.1 per cent (9.7 per cent for the biopsy specimen) in terms of fresh weight. These figures are quite different from those in the present case. The present case is the only one in which glycogenolytic enzyme studies were done.

It is by no means certain that in all of the cases of this subgroup the pathophysiologic features are identical. The degree of hypoglycemia, the curves for galactose and levulose tolerance and the severity of the clinical symptoms in these cases vary. It is possible to interpret these variations either as a result of differences in the degree of defect in metabolism or as the consequence of abnormalities of different enzyme reactions. In the absence of other enzyme studies than our own in this subgroup of cases, it is unwise to draw general conclusions regarding glycogenolysis in the liver.

Subgroup B: In this subgroup there are 11 cases (Biedermann and Hertz, case A;[15] Ellis and Payne, case 1 to 6;[16] Harnapp, case 2;[6b] Sundal;[17] Newns,[18] and van Creveld[1]). The only recorded galactose tolerance curve reported on was normal. In 2 cases the urine was examined after the administration of galactose. No sugar was found in 1, and a small amount was found in the other (Sundal[17] and van Creveld[1]). Of the 8 cases in which a levulose tolerance curve was recorded it was normal in 3 and low in 5. The dextrose tolerance curve was normal in 2 cases, flat in 1 and prolonged in 3. The level of blood

15. Biedermann and Hertz (footnotes 14 *g*, *h* and *i*).

16. Ellis, R. W. B., and Payne, W. W.: Glycogen Disease (von Gierke's Disease: Hepato(nephro)megalia Glycogenica), Quart. J. Med. **5**:31, 1936.

17. Sundal, A.: Glykogenosis (von Gierkes Krankheit), Acta pædiat. **19**:80, 1936.

18. Newns, G. H.: Hepatomegaly ? Case, Proc. Roy. Soc. Med. **30**:1069, 1937.

cholesterol was within the normal range in 7 cases. The level of inorganic phosphorus of the blood was low in several of the cases of Ellis and Payne but not in 3 other cases. In general, the clinical course gave evidence of less severe disease than in the cases of subgroup A. The hepatomegaly was first noted in infancy, but only 2 of the patients were studied in early infancy, the rest being observed between the ages of 4 and 18 years. The underdevelopment considered characteristic of glycogen disease was present, but the general health was fair. There is evidence of a familial incidence in the cases of both this subgroup and subgroup A. No autopsies and only 1 biopsy (Harnapp, case 2 [6b]) are reported to have been made in the cases of this subgroup. It does not appear possible on the available evidence to decide whether there existed in the cases in subgroup B metabolic defects comparable to those in subgroup A but less severe or other lesions, such as cirrhosis of the liver.

Subgroup C: This subgroup is composed of 2 cases which differ greatly from each other, although in both portions of the liver which were left in the ice box for many days retained all, or nearly all, of their glycogen. No detailed review of the postmortem observations in von Gierke's first case [2a] is needed. Unfortunately, no data are given in regard to blood sugar, urinary sugar or acetone. The case of Unshelm [2c] and Kimmelstiel [2d] appears to differ in many points from the other cases of von Gierke's disease, and it is retained in this subgroup on the basis of a single point, namely, the failure of the liver to autolyze its glycogen. The liver was large and contained glycogen, a fact which does not necessarily mean failure of glycogenolysis. There are many points in the case which are inconsistent with the concept that the glycolytic enzyme system was defective; the fasting blood sugar was normal (70 mg. per hundred cubic centimeters), and sugar was present in the urine. The liver was cirrhotic, and enzyme studies with liver tissue showed that when phosphate buffer was added the liver was able to break down glycogen in vitro in spite of the failure of autolysis, which suggests the possibility that the added phosphate contributed to the reaction. In our case the liver could not break down glycogen even in the presence of a phosphate buffer. It is difficult to regard this case as one of uncomplicated cirrhosis of the liver because of the large glycogen deposits and the failure of autolysis; it is also unwise to consider it a typical case of von Gierke's disease. The statement repeatedly found in the literature that the glycogenolytic enzymes of the liver are normal in cases of von Gierke's disease appears to be based chiefly on the data in this case. Glycogen was found in a number of unusual sites. The descriptions given suggest that some of the glycogen may have been smeared or may have diffused in the preparation of the slides. The ready solubility of glycogen makes this artefact common. In our preparations the sections of the liver and the kidney, both of

which contained large amounts of glycogen, showed a pale diffuse stain in the blood within the vessels and granules of glycogen in the connective tissue, while there was no glycogen in these locations in sections of tissues containing only small amounts of glycogen.

The studies by Kimmelstiel of the glycogen in this case led him to believe that it differed from the normal. His observations may be accepted without concluding from them that the glycogen is abnormal in all cases of von Gierke's disease. No abnormalities of the glycogen were found in our case or by Schönheimer [2b] in von Gierke's case. It appears reasonable to consider the case of Unshelm and Kimmelstiel as essentially dissimilar from the majority of cases of von Gierke's disease.

Subgroup D: There are 6 cases in which the clinical observations did not include the blood sugar curve after administration of epinephrine but in which the postmortem examination revealed an excess of glycogen in various organs, chiefly the liver and the kidney. Because of the absence of data on the response to epinephrine and of results of postmortem enzyme studies, these cases are not considered as instances in which the glycogen deposits are proved to be due to an inability of the liver to transform glycogen into dextrose, but the available evidence is compatible with this view. The cases included in this group are those of von Gierke, cases 2 [2a] and 3; [19] Faber; [2e] Krackower, cases 1 and 2 [14] and Esser and Scheidegger.[20]

COMMENT: The 34 cases we have cited are those which best fit the concept of disease resulting from a defective glycogenolytic enzyme system in the liver. Analysis of the data from the cases in this group, even though there has been some error in the selection of the cases, should reveal more consistent and more uniform characteristics than have been found in the entire series of cases in which there was an excess of glycogen in the liver. Correlation of clinical and pathologic data is unsatisfactory for the reason that careful clinical observations have rarely been reported for the cases in which adequate postmortem studies were made. The cases have been selected in part on the basis of failure of the level of blood sugar to rise on the injection of epinephrine. Another constant element is the value for fasting blood sugar, which lay between 20 and 70 mg. per hundred cubic centimeters in most of the 24 cases in which it was recorded; it was found to be over 80 mg. on one or more occasions in 8 cases. Variations in the tolerance curves after feeding dextrose, levulose or galactose have already been described.

19. von Gierke, E.: Ueber Glykogenspeicherungskrankheit, Beitr. z. path. Anat. u. z. allg. Path. **99**:369, 1937.

20. Esser, M., and Scheidegger, S.: Glykogenkrankheit, Schweiz. med. Wchnschr. **67**:970, 1937.

The urine contained various amounts of acetone in all of the 27 cases in which the subject is mentioned. Sugar was found in the urine in 2 of 23 cases.

Several points relating to the age-sex incidence are of interest. There is no significant difference in the sex incidence; cases in 17 males and in 15 females have been recorded. There is a suggestion of familial incidence in 5 cases but no indication that consanguinity was a factor. The age at which hepatomegaly was first noted is given in 24 cases: at birth, 10 cases; before the sixth month, 7 cases; between 6 and 12 months, 5 cases and in the remaining 2 cases at 2 years and 2 years 8 months of age. This uniformly early onset suggests that the disease is congenital.

Autopsies were performed in 10 cases. The ratio of the actual weight of the liver to the weight normal for the age varies from 2.72 to 5.50, with a mean of 3.74. Fat vacuoles were described in the liver cells in 8 of the 10 cases. The amount of fat was usually moderate but was 64.3 per cent of the dried weight in our case and 52.3 per cent in 1 of Krackower's cases.[141] We have no evidence as to whether the fat in the liver cells is due to transformation of ingested carbohydrates to fat or to a transfer of body fat to the liver. Another point of interest is the presence of deposits of glycogen in organs other than the liver. The amount present in most organs is not striking, but an increase in glycogen was consistently found in the kidney by microscopic examination. The weight of the kidney is recorded in 8 cases; in 2 of these the weight was normal for the age, while in the remaining 6 cases the weight was from 1.48 to 2.03 times normal. The percentage of glycogen is given in only a few cases, the largest figure being 6.53 per cent (von Gierke [2a]). The mechanism of the tendency to store glycogen is obscure. It may merely be an attempt on the part of the kidney to excrete the increased amount of glycogen present in the blood (van Creveld [1]), comparable to the deposits of hemoglobin present in the kidneys after massive hemolysis.

Group 2.—A case in this group has been previously reported and commented on by one of us.[21] Other cases which may be of the same nature are those of Langstein and Steinitz,[22] Göppert,[23] Reuss,[24] Fan-

21. Mason, H. H., and Turner, M. E.: Chronic Galactemia: Report of Case with Studies on Carbohydrates, Am. J. Dis. Child. **50**:359 (Aug.) 1935.

22. Langstein, L., and Steinitz, F.: Laktase und Zuckerausscheidung bei magendarmkranken Säuglingen, Beitr. z. chem. Physiol. u. Path. **7**:575, 1906.

23. Göppert, F.: Galactosurie nach Milchzuckergabe bei angeborenem, familiarem, chronischem Leberleiden, Berl. klin. Wchnschr. **54**:473, 1917.

24. Reuss, A.: Spontane Galaktosurie beim Säugling, Jahrb. f. Kinderh. **139**: 219, 1933.

coni [25] and Unshelm.[26] Work done in 1 case suggested that the defect in that case was probably in the enzyme system of the liver that converts galactose to glycogen. Thus the defect was comparable to that in the case we are reporting but involved another enzyme system. The result of this defect was that a large part of the absorbed galactose passed through the liver unchanged and entered the systemic circulation. This raised the total blood sugar to an abnormal level, and since the body could not remove the galactose from the blood, it removed the dextrose, until the latter reached an abnormally low level. If the patient in this case was fed ordinary amounts of milk as well as other food over any considerable period, the liver became extremely large. That part of this enlargement was due to glycogen was indicated by a normal response to epinephrine and by the fact that it took an unusually long period of fasting to make the patient excrete acetone.[21] When all milk was excluded from the diet the liver gradually returned to normal size.

Group 3.—The cases in this group are included for comparison with the cases of galactosuria, although there is usually no hepatomegaly, perhaps because the body can utilize levulose to some degree.[27]

Group 4.—In the cases included in this group the hyperinsulinism was the result either of a secreting tumor of the islands of Langerhans [28] or of large doses of insulin given because the patient had diabetes.[29] In the cases in which abnormal deposits of glycogen were found in the liver, the excess of insulin had been combated by the therapeutic administration of large amounts of carbohydrate, chiefly dextrose. It seems probable that the instability of the mechanism which regulates the supply of insulin would make for wide variations in the level of blood sugar, so that during postprandial periods of hyperglycemia the

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25. Fanconi, G.: Hochgradige Galaktose-Intoleranz (Galaktose-Diabetes) bei einem Kinde mit Neurofibromatosis Recklinghausen, Jahrb. f. Kinderh. **138**:1, 1933.

26. Unshelm, E.: Ueber die Glycogenkrankheit, Deutsche med. Wchnschr. **60**: 633, 1934.

27. Silver, S., and Reiner, M.: Essential Fructosuria: Report of Three Cases with Metabolic Studies, Arch. Int. Med. **54**:412 (Sept.) 1934. Marble, A., and Smith, R. M.: Essential Fructosuria, J. A. M. A. **106**:24 (Jan. 4) 1936. Edhem; Erden, F., and Steinitz, K.: Etudes sur un cas de lévulosurie essentielle, Acta med. Scandinav. **97**:455, 1938.

28. (*a*) Wilder, R. M.; Allen, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hyperglycemia, J. A. M. A. **89**:348 (July 30) 1927. (*b*) Seckel, H. P. G.: Postmortem Hepatic Glycogenolysis in Hyperinsulinism and Glycogen Disease, J. Clin. Investigation **18**: 723, 1939.

29. Brian, E. W.; Schecter, A. J., and Persons, E. L.: Unusual Glycogen Storage in Case of Diabetes Mellitus, Arch. Int. Med. **59**:685 (April) 1937. Friedman, N. B.: Insulin Hypoglycemia and Glycogenic Hepatomegaly in Diabetes Mellitus, Arch. Path. **29**:414 (March) 1940.

excess of sugar would be stored in the liver as glycogen. Seckel [28b] has demonstrated values for liver glycogenolysis within the normal range. Cases in this group do not appear to be readily confused with the ones previously described.

Group 5.—This group is heterogeneous, composed largely of cases which cannot be assigned to the groups previously mentioned because of inadequate data and of cases in which there is some doubt that there was an excess of glycogen in the liver.

Subgroup A: This subgroup includes cases in which the injection of epinephrine resulted in a rise of over 40 mg. per hundred cubic centimeters in blood sugar and in which the urine contained acetone but no reducing substance. Six such cases have been found.[30] Biopsy was performed in 1 [30d] and autopsy in another.[8] In both instances an excess of glycogen and cirrhosis of the liver were found. Hepatomegaly was first noted in infancy in all of them, and in 4 hypoglycemia was shown on fasting. The sugar tolerance curves vary greatly. It is not certain that the cases are uniform with respect to the pathologic change. The presence of a moderate degree of cirrhosis in association with heavy deposits of glycogen is difficult to interpret. Since the glycogen can be readily mobilized from the liver by the injection of epinephrine, the fundamental defect appears to be elsewhere than in the glycogenolytic enzyme system of the liver.

Subgroup B: In this subgroup are included the several cases in which there were clinical and pathologic manifestations of von Gierke's disease but in which glycogen was not demonstrated in the organs at autopsy. These are the cases of Kramer, Grayzel and Solomon [31] and of Debré and Semelaigne.[32] The cases of Björum [33] and of Bellingham-Smith and O'Flynn [34] may also belong here. In view of the ease with

30. (*a*) Watson, P., and King, A.: Hepatomegaly: ? Von Gierke's Disease, Proc. Roy. Soc. Med. **28**:150, 1934. (*b*) Rauh, L., and Zelson, C.: Disturbance in Glycogen Metabolism with Hepatomegaly, Am. J. Dis. Child. **47**:808 (April) 1934. (*c*) Wilder, R. L.: A Case of Hepatonephromegalia Glycogenica: Von Gierke's Glycogen Storage Disease, J. Pediat. **7**:214, 1935. (*d*) Paradiso, F.: Contributo clinico-istologico allo studio della malatta glicogenica nel bambino, Pediatria **46**:32, 1938. (*e*) Harnapp.[6b] (*f*) Lindsay, Ross and Wigglesworth.[8]

31. Kramer, B.; Grayzel, H. G., and Solomon, C. I.: Chronic Hypoglycemia in Children, J. Pediat. **5**:299, 1935.

32. (*a*) Debré, R.; Semelaigne, G.; Nachmansohn and Gilbrin: Les hépatomégalies polycoriques, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1023, 1934. (*b*) Debré, R., and Semelaigne, G.: L'hépatomégalie polycorique, Presse méd. **43**:857, 1935; (*c*) footnote 10.

33. Björum, A.: The Occurrence of Fatty Liver in Families, Acta pædiat. **6**: 225, 1926.

34. Bellingham-Smith, E., and O'Flynn, E.: Familial Hepatomegaly of Uncertain Pathology, Lancet **1**:297, 1933.

which glycogen sometimes disappears when tissues are fixed in aqueous solutions, it is not impossible that these are true cases of glycogen disease. No description of the method of fixation of the tissues is given. The presence of an abundance of fat in the liver in these cases does not militate against the diagnosis, as is demonstrated in our case.

Subgroup C: There are 7 cases in which the clinical studies did not include an epinephrine curve and in which no postmortem examination was made. These are the cases of Unshelm, case 1,[2c] Solomon and Anderson,[35] Beumer [36] and Naish and Gumpert [37] and the 3 cases of Exchaquet.[38] No conclusions can be drawn in regard to them on the basis of our criteria.

Subgroup D: There remains a group of cases in which there was hepatomegaly but in which the urine contained no acetone. One of these appears to be a case of cirrhosis of the liver (Neuteboom,[39]). Fliess and Bloom [40] reported a case of nephrosis with hepatomegaly in which acetone was found only during the height of the nephrosis. There is no clear evidence in either of these cases that the hepatomegaly was due to deposits of glycogen. In the case of Chrometzka and Brunssen [9] there were a fasting blood sugar of 72 mg. per hundred cubic centimeters, a level of blood cholesterol within the normal range, and no glycosuria or acetonuria, but an excess of glycogen in the liver was demonstrated at autopsy. The liver also showed cirrhosis. Enzyme studies showed splitting of glycogen by the liver and a moderate degree of glycogenolysis in autolysis experiments. This does not appear to be a case of von Gierke's disease, and the diagnosis of cirrhosis of the liver is compatible with the data. The cases of Goldman [11] (except case 1) are somewhat similar. Three children in a family of 8 had enlarged livers; 1 died at 2½ years of age and was found to have cirrhosis of the liver, with diffuse fatty infiltration. Another, studied at 1½ years of age, had blood sugar curves after the administration of dextrose,

35. Solomon, H. J., and Anderson, P. M.: A Case of von Gierke's "Glycogen Accumulation Disease," M. J. Australia **2**:660, 1933.

36. Beumer, H.: Ueber den Cholesterinstoffwechsel bei Glykogenspeicherkrankheit, München. med. Wchnschr. **84**:1007, 1937.

37. Naish, A. E., and Gumpert, T. E.: Von Gierke's Disease Associated with Amylorrhoea, Brit. M. J. **1**:360, 1936.

38. Exchaquet, L.: Infantilisme hépatique familial, Arch. de. méd. d. enf. **34**: 657, 1931.

39. Neuteboom, J. J.: Zur Kenntnis der Glykogenkrankheit (Hepatomegalia glykogenica: von Gierke-van Creveld; Cardiomegalia glycogenica: Pompe), Klin. Wchnschr. **17**:1437, 1938.

40. Fliess, M. M., and Bloom, S. M.: Von Gierke's Glycogen Storage Disease: Case Report with Unusual Findings, J. Pediat. **12**:635, 1938.

epinephrine and insulin which were within the normal range. In neither case was glycosuria or acetonuria found. The evidence appears inadequate for the diagnosis of von Gierke's disease. Debré and Semelaigne's fourth case is similar. The clinical and pathologic criteria are inadequate for classification in the cases of Worster-Drought [41] and in Debré and Semelaigne's [32b] second and third cases, in none of which was acetonuria present.

DIVISON II: *Group 1.*—Eleven cases have been found in which the presence of grossly abnormal amounts of glycogen was demonstrated in the heart muscle either by Best's stain or by chemical analysis.[42] There are in addition many cases in which the course and pathologic data were similar but in which the nature of the substance in the cardiac muscle fibers was not proved; it is highly probable that these cases are actually cases of glycogen deposition in the heart, since with 1 exception the disease presents a uniform picture, in contrast to that in the cases of glycogen deposition in the liver. Ten of the 11 proved cases were of infants who died between the ages of 5 weeks and 8 months of progressive cardiac failure, often complicated by bronchopneumonia. The eleventh case [42k] was one of sudden death in a boy of 11 years and appears to deserve a separate category. The sex is noted in 8 of the 10 cases in infants: Five patients were girls and 3 boys. In addition to the cardiac symptoms, 2 infants had macroglossia,[43] which led to a

41. Worster-Drought, C., and Weber, F. P.: Hepatomegaly with Persistent Ketonuria in a Child, Brit. M. J. **1**:403, 1933. Worster-Drought, C.: Hepatomegaly with Persistent Ketonuria, Proc. Roy. Soc. Med. **28**:829, 1935.

42. (*a*) Pompe, J. C.: Hypertrophie idiopathique du cœur, Ann. d'anat. path. **10**:23, 1933. (*b*) Bischoff, G.: Zum klinischen Bild der Glykogenspeicherungkrankheit (Glykogenose), Ztschr. f. Kinderh. **52**:722, 1932. (*c*) Putschar, W.: Ueber angeborene Glykogenspeicherkrankheit des Herzens. "Thesaurismosis glycogenica" (von Gierke), Beitr. z. path. Anat. u. z. allg. Path. **90**:222, 1932. (*d*) Humphreys, E. M., and Kato, K.: Glycogen-Storage Disease, Thesaurismosis Glycogenica (von Gierke), Am. J. Path. **10**:589, 1934. (*e*) Antopol, W.; Heilbrunn, J., and Tuchman, L.: Enlargement of the Heart Due to Abnormal Glycogen Storage, Am. J. M. Sc. **188**:354, 1934. (*f*) Hertz, W., and Jeckeln, E.: Glycogenspeicherkrankheit unter dem klinischen Bilde des Myxödems, Ztschr. f. Kinderh. **58**:247, 1936. (*g*) Hertz, W.: Untersuchungen über den vitalen und postmortalen Kohlehydratstoffwechsel bei Glykogenose und gestörter Schilddrüsentätigkeit, ibid. **58**:259, 1936. (*h*) Wolff, K.: Beitrag zur Morphologie und Chemie der Glykogenspeicherkrankheit, Beitr. z. path. Anat. u. z. allg. Path. **97**:289, 1936. (*i*) Mutgeert, B. L.: Congenital Cardiac Hypertrophy, Especially in Connection with Glycogen Storage Disease, Maandschr. v. kindergeneesk. **6**:233, 1937. (*j*) Mansens, B. L.: Idiopathic Hypertrophy of Heart, Diffuse Rhabdomyomatosis and Glycogen Storage Disease, ibid. **6**:246, 1937. (*k*) Gardner, E., and Simpson, K.: Sudden Death from von Gierke's (Glycogen) Disease, Lancet **1**:659, 1938. (*l*) van Creveld.[1]

43. Hertz and Jeckeln.[42f] Wolff.[42h]

diagnosis of myxedema in 1 case. Postmortem examination revealed that the macroglossia was due to the deposit of large amounts of glycogen in the muscle fibers. Clinical laboratory studies are few; in the 2 cases in which observations were made on fasting blood sugar and blood sugar curves after the administration of epinephrine, the values were normal.[44] This is of great interest as evidence that the fundamental metabolic difficulty is not the same as in cases of von Gierke's disease. In 1 of these cases [42f] the dextrose tolerance curve was flat; in the other it was said to be biphasic.[42g] In the latter the galactose tolerance curve was also biphasic. The urine contained no sugar (3 cases), no acetone (3 cases) and no diacetic acid (1 case). The absence of acetone in the urine is again in contrast to its occurrence in cases of von Gierke's disease. The value for blood cholesterol was 115 mg. per hundred cubic centimeters in 1 case, and the level of blood glycogen was normal in 1 case. At autopsy the heart showed uniform extreme hypertrophy of the myocardium, and the liver was either of normal size or slightly enlarged. Some measurement of the amount of glycogen in the heart muscle has been made in 5 of the cases. In 1 the heart retained 3.57 per cent of glycogen after remaining for a period in solution of formaldehyde U. S. P.; in 3 there was between 7.9 and 10 per cent of glycogen in terms of fresh weight, and in 1 glycogen constituted 33.2 per cent of the dried weight. There was also an increase in the glycogen content of both smooth muscle (4 cases) and striate muscle (5 cases). The liver contained from 3 to 9 per cent of glycogen (fresh weight) in 4 cases and 11.7 per cent (dried weight) in 1 case. The tongue contained 35.2 per cent of glycogen (dried weight), or slightly more than the myocardium, in Wolff's case, and the skeletal muscle contained 9.39 per cent of glycogen (wet weight) in van Creveld's case. The smooth muscle which was the site of glycogen deposit was in most instances that of the arterial walls, although the trachea, the stomach and the bladder have also been mentioned. The intestinal muscle contained no glycogen in 2 cases. A moderate deposit of fat in the liver was mentioned once. Postmortem studies of glycogenolysis in vitro were made by Herz and Jeckeln and by van Creveld, who demonstrated unusual stability of the heart glycogen. The former demonstrated some increase in glycogenolysis on incubation with a phosphate; the latter found marked loss of glycogen on mixing the heart muscle with heart muscle from another patient.

Comparison of the data in these 10 proved cases of glycogen deposition in the heart with the cases of von Gierke's disease leads to the conclusion that in both diseases there is an abnormality in the enzyme reactions involved in glycogenolysis rather than in the glycogen itself.

44. Hertz and Jeckeln.[42f] Mansens.[42j]

Evidence that the specific defect in the chain of enzyme reactions is different in the two groups of cases is considered later.

Group 2.—There remain 2 cases in which the main deposits of glycogen were in the muscle but which differ from the previously discussed cases and from each other. One of these has been mentioned,[42k] that of the 11 year old school boy who died suddenly, without previously noted symptoms, and was found to have a large heart loaded with glycogen. No explanation is offered for this case. The other is the case of Günther,[45] that of an infant who was thought to have amyotonia congenita. Postmortem examination at the age of 11 months demonstrated massive depositis of glycogen in the striate muscle fibers. This may have been a case of glycogen disease of the heart in which the deposits of glycogen in the striate muscle were especially pronounced, or it may represent a distinct disease, with a different metabolic anomaly.

CLASSIFICATION OF CASES FROM THE LITERATURE IN WHICH THERE WAS EXCESSIVE STORAGE OF GLYCOGEN

From this collection of cases, we believe, the following five groups can be separated clinically and pathologically.

1. Glycogen storage disease of the liver (true von Gierke's disease), which we believe is due to a defect, probably congenital, in one portion of the enzyme system of the liver which performs the conversion of glycogen to dextrose and dextrose to glycogen. In these cases the liver appears to have no difficulty in converting levulose, galactose and the other precursors of liver glycogen except dextrose to glycogen. Clinically, the patients in this group of cases show early hepatomegaly, little or no rise in the level of blood sugar after the administration of epinephrine and marked tendency to ketosis. At autopsy the liver contains large amounts of glycogen, which it is unable to break down in vivo or in vitro, even with the addition of buffer. The other organs may or may not contain abnormal amounts of glycogen. When the defect involves the conversion of dextrose to glycogen, there should be a high, prolonged dextrose tolerance curve and normal or low levulose and galactose tolerance curves, as in our case. This group includes most of the cases in group 1, division I.

2. Glycogen storage disease of the heart and muscles. We are inclined to believe that in this group the defect is similar but is present at another point in the enzyme system. All muscle makes glycogen from dextrose but does not change glycogen back to dextrose. When glycogen is broken down in muscle, it is mainly converted either to lactic acid or to carbon dioxide and water. If the defect in these cases

45. Günther, R.: Beitrag zur Kenntnis der Glykogenspeicherkrankheit, Virchows Arch. f. path. Anat. **304**:87, 1939.

were the same as that postulated for group 1, the formation of glycogen from dextrose would be blocked but the normal breakdown of glycogen would not be blocked. The reverse is apparently true: These hearts can make glycogen from dextrose but cannot adequately break down glycogen. Therefore we suggest that the probable site of the defect is outside the mechanism of converting dextrose to glycogen, possibly in that of converting hexose 6-phosphate to lactic acid or of the latter to carbon dioxide and water. This defect is congenital. Clinically, the patients in this group of cases show progressive cardiac decompensation and enlargement of the heart. In contrast to patients with glycogen disease of the liver, they show a normal response to epinephrine and do not have a tendency to ketosis. Furthermore, almost all the patients die within their first year. This group contains all of the cases in division II.

3. A third group of cases includes those in which there is galactosuria, which is probably due to a defect in the enzyme system of the liver that converts galactose to glycogen or, what seems less likely, directly to dextrose. The patients in these cases show retarded physical development and extremely large livers early in life. The urine contains albumin and, during the postprandial periods, galactose. A milk-free diet relieves them of all symptoms and reduces the size of the liver. They respond normally to epinephrine and excrete ketones only after prolonged fasting. This group contains the cases in group 3, division I.

4. In a fourth group of cases, the excess deposition of glycogen is due to the secretion or administration of excessive amounts of insulin and the ingestion of large amounts of carbohydrate. Both factors must be present. There is no evidence that the enzyme systems of either the liver or the muscle are defective in this group. The patients respond normally to epinephrine and show no unusual tendency to ketosis. The liver may be extremely large. At autopsy the liver contains more than the normal amount of glycogen. Seckel has shown that in these cases the liver is capable of breaking down glycogen in vitro. These are the cases in group 4, division I.

5. In a fifth group there are hepatomegaly and delayed development but little disturbance of the response to epinephrine and no abnormal tendency to ketosis. Blood sugar tolerance curves after the ingestion of galactose or dextrose are apt to be higher and more prolonged than normal. At autopsy the liver shows larger glycogen stores than normal, but enzyme studies in the few cases in which these have been carried out have shown that the liver is able to break down glycogen. Furthermore, in many of these cases the liver shows well marked cirrhosis. It is well known that cirrhosis impairs the ability of the liver to metabolize galactose, but less is known about its effect on the metabolism of dextrose. For the time being it seems best to

recognize that there is this group of cases that do not qualify for any one of the previous groups and that in most of them cirrhosis is shown at autopsy.

The remaining cases we are unable to classify. The clinical and pathologic evidence presented is insufficient in many respects. As time goes on, other conditions may come to light that will bring about a similar picture.

SUMMARY

A case of glycogen storage disease of the liver has been reported, with clinical and postmortem studies which we believe place the fundamental defect in the enzyme system of the liver which performs the conversion of glycogen to dextrose and dextrose to glycogen.

The cases reported as glycogen storage disease (von Gierke's disease) have been analyzed, and five groups of cases, each dependent on a different fundamental defect, have been separated by clinical and pathologic criteria.

Dr. Hans T. Clark, Dr. Edward G. Miller Jr. and Dr. G. L. Foster, of the department of Biological Chemistry, Columbia University College of Physicians and Surgeons, gave advice and cooperation in this study.

News and Comment

GENERAL NEWS

Second American Congress on Obstetrics and Gynecology.—The Second American Congress on Obstetrics and Gynecology will be held in St. Louis, April 6 to 10, 1942. All of the meetings and the commercial and educational and scientific exhibits will be held in the public auditorium.

The following committees, with their chairmen, have been appointed: executive, Dr. Fred L. Adair, Chicago; program, Dr. E. D. Plass, Iowa City; motion picture, Dr. Robert D. Mussey, Rochester, Minn.; educational and scientific exhibits, Dr. H. Close Hesseltine, Chicago; commercial exhibits, Dr. Philip F. Williams, Philadelphia; lay publicity, Dr. Joseph L. Baer, Chicago; professional publicity, Dr. George W. Kosmak, New York; publications, Dr. Goodrich C. Schauffler, Portland, Ore.; evening meetings, Dr. Robert L. De Normandie, Boston; membership, Dr. Buford G. Hamilton, Kansas City, Mo., and budget and finance, Dr. William C. Danforth, Evanston, Ill.

The general plan for the program will be much the same as that of the first congress, which was held in Cleveland, Sept. 11 to 15, 1939, with sectional meetings for the various groups (nurses, public health workers, administrators, educators and physicians), general sessions for all members attending the congress and round tables. There will be evening sessions open to the general public.

Adequate time for registration will be given the first day, before the opening of the sessions of the congress. Admission will be by individual membership card only. Such cards may be secured by payment of the $5 registration fee, any time after Sept. 1, 1941.

At the suggestion of the Medical Exhibitors' Association, more time will be allowed for the members of the congress to visit the exhibits. The response of the firms handling products of interest to obstetricians and gynecologists to a letter announcing the second congress has been admirable, and excellent commercial exhibits are assured.

Hotel headquarters have not been assigned to the various groups as yet, but the medical section and the general headquarters of the congress will be in the Jefferson Hotel.

Further information may be secured from the Chicago office of the congress, at 650 Rush Street.

The American Board of Pediatrics.—The examination at Boston will be held on Oct. 7 and 8, 1941, instead of on October 12. A written examination for the group scheduled to take the oral examination in Boston will be held locally, under a monitor, on August 22.

PERSONAL NEWS

Dr. William E. Ladd Appointed.—Dr. William E. Ladd, clinical professor of surgery at the Harvard Medical School and chief of surgical services at the Children's Hospital, Boston, has received the first appointment to the William E. Ladd professorship of surgery, a chair which has been permanently endowed by his friends and associates. This is the first Harvard professorship devoted exclusively to child surgery.

Abstracts from Current Literature

Vitamins; Avitaminoses

CUTANEOUS MANIFESTATIONS OF VITAMIN A DEFICIENCY IN CHILDREN. EDWARD LEHMAN and HOWARD G. RAPAPORT, J. A. M. A. **114**:386 (Feb. 3) 1940.

Symmetric dry areas of follicular keratoses on the extremities of 9 indigent children showing evidence of vitamin A deficiency by photometric tests are described. Large doses of vitamin A in courses of varying duration improved the skin and the night blindness. Ichthyosis follicularis in some cases may be due to avitaminosis A. Reports of this have been chiefly from oriental countries and have infrequently concerned children. The minimum intake is estimated at about 20 to 30 units per kilogram of body weight per day.

HEERSMA, Kalamazoo, Mich.

CEREALS AND RICKETS: X. THE AVAILABILITY OF PHYTIC ACID PHOSPHORUS. CARL H. KRIEGER, RUDOLF BUNKFELDT and HARRY STEENBOCK, J. Nutrition **20**:7 (July) 1940.

These Wisconsin investigators noted that the utilization of phosphorus from phytic acid was not equal to that of inorganic phosphorus. Vitamin D enhanced the utilization of phosphorus from phytic acid and produced a less marked effect on the utilization of inorganic phosphorus. With the food consumption almost identical, the rats receiving the inorganic phosphorus, even without vitamin D, were definitely superior to those receiving the same amount of phosphorus as of phytic acid with and without vitamin D.

FREDEEN, Kansas City, Mo.

EFFECT OF FLUORINE ON THE ACTIVITY OF VITAMIN D IN RACHITIC RATS. KENNETH MORGAREIDGE and SIDNEY B. FINN, J. Nutrition **20**:75 (July) 1940.

There appeared to be a decrease in the severity of rickets when rats were given a rachitogenic diet containing fluorine. Morgareidge and Finn believe that this was due to a general increase in the density of the bones roentgenographically, with a decrease in the width of hypertrophic cartilage of the metaphysial zone.

Apparently fluorine had interfered with orderly arrangement of the matrix cells, since the deposition of new bone salt was atypical when vitamin D was given to heal this "fluorine rickets."

The healing process was inhibited when fluorine and vitamin D were given simultaneously to rachitic rats which had not previously had fluorine poisoning. The inhibition was roughly proportional to the dose of fluorine given (i. e., amounted to 50 per cent at the level of 3 mg. of fluorine per day).

FREDEEN, Kansas City, Mo.

THE RELATIONSHIP BETWEEN BIOPHOTOMETER TESTS AND THE VITAMIN A CONTENT OF THE BLOOD OF CHILDREN. WILLIAM S. BAUM and AUGUSTA B. MCCOORD, J. Pediat. **16**:409 (April) 1940.

A group of patients from the pediatric service of the Strong Memorial Hospital and the Rochester Municipal Hospital were tested with the biophotometer, and the results were correlated with the vitamin A content of the blood. Ninety-eight subjects were tested once with the biophotometer. Nineteen of this group showed subnormal dark adaptation by Jean's standard. Seventy of the children

from whom a dietary history was obtained showed no correlation between diet and biophotometer readings. No history of subjective symptoms of vitamin A deficiency could be elicited. Correlation was absent between all readings of the biophotometer and the vitamin A, carotene and xanthophyll content of the blood. Nineteen patients were subjected to repeated testing with the biophotometer until no further improvement in readings occurred. A decrease in the number of subnormal readings was found after repeated testing. No statistically significant correlation was found between the concentration of vitamin A in the blood and the postbleaching biophotometer reading. A single reading on the biophotometer is of no value in estimating vitamin A deficiency. RAUH, Cincinnati.

CAPILLARY FRAGILITY AND ASCORBIC ACID STUDIES. H. G. RAPAPORT, S. H. MILLER and A. SICULAR, J. Pediat. **16**:624 (May) 1940.

Determinations of the vitamin C content of the blood plasma and capillary fragility tests were made for 150 children, 41 of whom had some stigmas of rheumatic disease. A blood plasma level of vitamin C from 0.7 to 2 mg. per hundred cubic centimeters was considered normal and a level below 0.7 mg. subnormal. Wright's standard of capillary fragility was accepted; ten or less petechiae were considered normal; from ten to twenty, borderline, and twenty or more, evidence of capillary fragility. Forty per cent of the series were found to have a normal level of ascorbic acid in the blood plasma and a normal capillary fragility. A normal level of ascorbic acid and an abnormal capillary fragility were found in 21.3 per cent. A subnormal level of ascorbic acid and a normal capillary fragility occurred in 27.3 per cent. Subnormal figures for ascorbic acid blood plasma level with a positive result from the fragility test were found in 11.3 per cent. These results showed parallelism in 51 per cent of the cases, whereas in 49 per cent a discrepancy existed between the result of the capillary fragility test and the level of ascorbic acid in the plasma. RAUH, Cincinnati.

A TEST PROPOSED TO MEASURE VITAMIN B_1 SATURATION IN HUMANS. H. POLLACK, H. DOLGER, M. ELLENBERG and S. COHEN, Proc. Soc. Exper. Biol. & Med. **44**:98 (May) 1940.

One milligram of thiamine hydrochloride was injected into each of 349 unselected patients in a fasting state, and the urine was collected for a four hour period following the injection. The vitamin B_1 activity of this collected urine was assayed by means of the Schultz, Atkins and Fry yeast fermentation of dextrose test. By the average normal person 180 gamma or more is excreted in the four hour interval, and patients excreting less than this may be considered as showing below average saturation. Forty-eight patients with gastrointestinal and cardiac disease excreted less than did 35 normal healthy adult subjects. The results of excretion studies of 13 patients with diabetes mellitus revealed no abnormality in this group. HANSEN, Minneapolis.

ACTION AND TOXICITY OF VITAMIN B_6 HYDROCHLORIDE. C. G. WEIGAND, C. R. ECKLER and K. K. CHEN, Proc. Soc. Exper. Biol. & Med. **44**:147 (May) 1940.

Studies were made of the degree of potency and toxicity of crystalline vitamin B_6 hydrochloride. Forty to 60 gamma cured acrodynia in rats within fourteen days. The median lethal dose for mice was 545.3 ± 42.9 mg. per kilogram and for rats 657.5 ± 18.3 mg. per kilogram. Doses of 100 mg. per kilogram repeated intravenously in mice for two weeks failed to interfere with their normal gain in weight. Twelve normal men were given 100 to 200 mg. of the drug either by mouth or intravenously, with no ill effects. Pain occurred when vitamin B_6 was given intramuscularly. HANSEN, Minneapolis.

PYRUVIC ACID IN BLOOD AND CEREBROSPINAL FLUID. E. BUEDING and H. WORTIS, Proc. Soc. Exper. Biol. & Med. **44**:245 (May) 1940.

Samples of blood and spinal fluid were obtained simultaneously from 67 patients with various neuropsychiatric and medical disorders, at rest in bed and fasting, and the pyruvic acid content was determined. The pyruvic acid content of the blood varied from 0.77 to 1.16 mg. per hundred cubic centimeters, and values of 1.30 mg. or over were considered abnormally high. The pyruvic acid in the cerebrospinal fluid was but 70 to 120 per cent of that found in blood taken simultaneously. In 16 cases the values for blood pyruvate were high, and in 13 of these definite clinical evidence of vitamin B_1 deficiency was present. In the other 3 subclinical states may have existed.

HANSEN, Minneapolis.

REGARDING SUPPLY OF VITAMIN B TO THE INFANT. K. SCHWARTZER and H. REINHARDT, Med. Klin. **35**:817 (June 16) 1939.

Cow's milk is a richer source of vitamin B than is breast milk, but with dilute formulas the vitamin B intake may be low. Autoclaving destroys the vitamin. Vitamin B is synthesized by Bacillus bifidus in the colon of the breast-fed infant, but it is not absorbed.

SIEMSEN, Chicago.

DOES ULTRAVIOLET IRRADIATION OF MILK DECREASE THE VITAMIN C CONTENT? K. SCHEER, München. med. Wchnschr. **86**:603 (April 21) 1939.

There is a slight decrease in the vitamin C content of milk following irradiation with ultraviolet rays. However, it is of no practical significance. The vitamin C content of milk is so low that the infant must receive a supplementary supply for proper nutrition.

BRAHDY, Mt. Vernon, N. Y.

VITAMIN B CONTENT OF COW'S AND BREAST MILK. F. WIDENBAUER and F. HECKLER, Ztschr. f. Kinderh. **60**:683 (April 1) 1939.

The work of other authors is discussed, as well as methods of determining vitamin B. Although cow's milk has a higher content of vitamin B (13 to 57 micrograms per hundred cubic centimeters) than has breast milk (2 to 36 micrograms per hundred cubic centimeters), the amount in breast milk is apparently entirely adequate for the infant. Supplementary feeding of vitamin B to nursing mothers has practically no influence on the amount of the vitamin secreted in breast milk, because the diet is usually adequate in vitamin B. Excess is excreted in the urine. Studies of the blood serum show that vitamin B in breast milk is secreted rather than diffused.

SIEMSEN, Chicago.

EXPERIMENTAL AVITAMINOSIS A IN MAN. KARL-HEINZ WAGNER, Ztschr. f. physiol. Chem. **264**:153 (May 28) 1940.

An extensive and comprehensive study was made on 10 human subjects from 23 to 57 years of age, who voluntarily subsisted on a diet practically free of vitamin A but otherwise complete for two hundred and ninety-three days. The diet was tested by rat feeding experiments. Readings with an adaptometer (Nagel type) were made throughout the course of the study, and the findings were compared with those on 20 control subjects. After one hundred and eighty-eight days the following observations were made. The adaptometer values were 3,500 to 6,000 as compared with the normal value of 130,000. There was an inversion of diminution of the visual fields for red and blue, and all the subjects had shrinking of the visual field for yellow. After six months there was a definite decrease in the weight of all subjects on the diet. A decrease in hemoglobin and in the erythrocyte count was noted, and later, poikilocytosis and anisocytosis. Leukopenia developed, with degeneration present in the cells of the myeloid series. A decided decrease took place in the thrombocytes. Only 1 person had a platelet count of

110,000, whereas the lowest was but 30,000, and all were definitely lower than the previous values, which had been in the neighborhood of 400,000 to 500,000. On refeeding vitamin A, it appeared that the minimal requirement was 2,000 international units daily, while the average was 2,500 international units daily. It was necessary to use 5,000 international units of beta carotene to obtain the same healing effect as was obtained with vitamin A. Studies of the absorption and retention of vitamin A were performed by examination of the blood and also by tests of the stool and of the urine.

HANSEN, Minneapolis.

BERI-BERI (AVITAMINOSIS B) IN AN INFANT. T. VARGA, Orvosi hetil. **83**:38 (Jan. 14) 1939.

A 14 month old child was admitted to the child clinic at Szeged, Hungary, with the history that it had had diarrhea for two weeks and that a physician had prescribed rice soup for twenty-four hours. The mother gave rice soup only for two weeks. At the end of the two weeks the child's legs were swollen, and edema had appeared around the eyes. Both eyes showed horizontal nystagmus, and the right eyelid was ptotic. There was decided cervical opisthotonos, but the lumbar puncture showed normal conditions. The extremities were cyanotic. The pulmonary second sound was loud. The infant then was given protein milk and 25 Gm. of yeast daily. The edema and the cyanosis disappeared in two weeks, the appetite improved, and the neurologic symptoms began to disappear after the third week.

GÖTTCHE, Budapest, Hungary.

DIAGNOSIS OF LATENT A AVITAMINOSIS BY BIOPHOTOMETER. C. SEKI, H. BIN and K. NAGAO, Acta pædiat. japon. **45**:1462 (Oct.) 1939.

By means of a biophotometer the authors tested dark adaptation in 100 primary school children of the higher social strata and 50 of the lower. It was found that there was evidence of A avitaminosis in both groups but children of the lower stratums showed a higher percentage (40 per cent) than those of the higher stratums (6 per cent). In an examination of 80 nurses in the Keijo University Hospital latent A avitaminosis was detected in 7.5 per cent. When cod liver oil was administered in adequate amounts, the dark adaptation test gave normal results.

KATO, Chicago.

HISTOCHEMICAL AND BIOCHEMICAL STUDIES OF PHOSPHATASE IN EXPERIMENTAL RICKETS. S. KODAMA, Acta pædiat. japon. **45**:1464 (Oct.) 1939.

Glycerophosphatase in the serum, as determined by the method of Izumi-Takamatsu, was greatly increased in experimental rickets (rabbits), reaching the maximum in seven to eight weeks after the institution of a synthetic rachitogenic diet (Fujimaki). Histochemically this enzyme was increased most strikingly at the ends of the long bones and moderately in the intestinal tract, liver and kidneys, while the adrenal glands showed only a slight increase.

The histochemical demonstration of phosphatase, according to the method of Izumi and Takamatsu, depends on the formation of calcium phosphate in a tissue section which has been immersed in a solution containing calcium ion and ester phosphorus at an optimal hydrogen ion concentration. When a section so prepared is tested according to the silver nitrate method of Kossa, the portion of the section containing phosphatase takes on a yellowish brown color which can easily be demonstrated under the microscope.

FECAL EXCRETION OF VITAMIN B_1 IN INFANTS. S. MORI and M. TURUDA, Acta pædiat. japon. **45**:1477 (Oct.) 1939.

Using the modified method of Ritsert, Mori and Turuda estimated the daily fecal excretion of vitamin B_1 by infants and found the values to lie between 20 and 60 micrograms, with an average of 33 micrograms. After administration

of 500 micrograms of the vitamin, the fecal excretion during the first and second days was 79 and 47 micrograms, respectively, with a return to the normal 21 micrograms on the third day.

KATO, Chicago.

METABOLISM OF VITAMIN B_1. T. TAKAI and T. TAKEHARA, Acta pædiat. japon. **45**:1478 (Oct.) 1939.

The colorimetric method of Hongo was used in estimating the vitamin B_1 content of processed and fresh pasteurized milk. From the results obtained it is concluded that these types of milk do not differ significantly in content of vitamin B_1. An examination of various commercial preparations of vitamin B_1 (for intravenous use) revealed considerable difference in vitamin B_1 content, ranging from 0.21 to 4.80 mg. per cubic centimeter of solution. The daily urinary excretion of vitamin B_1 by infants and children fluctuated between 8 and 55 micrograms. The saturation test showed the maximal excretion during the first day following peroral administration of 25 mg. of vitamin B_1 in normal healthy children, while the maximum excretion was obtained on the second day in children with nephritis and tuberculosis, the peroral dosage being 50 mg. in both groups of patients.

KATO, Chicago.

VITAMIN B_1 IN HUMAN URINE. K. HIRAI and H. IDE, Acta pædiat. japon. **45**:1482 (Oct.) 1939.

In a study of infants, Hirai and Ide used the thiochrome method of Jansen as improved by Hongo to determine the daily urinary excretion of vitamin B_1 in both normal and pathologic conditions. In conditions of health the daily excretion was found to vary from 10 to 50 micrograms, and in pathologic conditions the variations ranged from 0 to 80 micrograms. In an infant fed by a wetnurse for a period of three days, the daily excretion of vitamin B_1 amounted to 19, 0 and 1.4 micrograms, respectively, and the vitamin B_1 content of this nurse's milk gave the following figures: 107, 43 and 97 micrograms, respectively.

KATO, Chicago.

VITAMIN A AND RESPIRATORY INFECTIONS. M. UDDSTRÖMER, Acta med. Scandinav. **102**:214, 1939.

After a survey of the literature, the author reports his own observations. In an industrial district of Sweden where unemployment was a serious problem for several years and continued to be during the period of study, minimum perception of light was studied in 783 school children. Judged by this criterion, 10.2 per cent of them suffered from vitamin A deficiency. Six hundred of them were reexamined six months later, and all were found normal. The only explanation was in the "free school meal," which supplied an average of 1,450 international units of vitamin A daily to every child. One half of the children received an additional 8,000 international units of vitamin A. No significant difference was observed in the incidence of respiratory infections or in the growth of these children, indicating that an intake of vitamin A above the requirement does not give further beneficial effects.

KAJDI, Baltimore.

VITAMIN C IN THERAPY. M. VAN EEKELEN, Nederl. tijdschr. v. geneesk. **83**:4015 (Aug. 12) 1939.

Van Eekelen reviews the various clinical applications of ascorbic acid and the reasons which have led to its use. He considers the criteria to be followed in deciding to use vitamin C therapy and makes special mention of the value of the vitamin C level of the blood. The advantages and disadvantages of the various routes of introduction of the vitamin (parenteral and oral) are discussed.

VAN CREVELD, Amsterdam, Netherlands.

Hygiene; Growth and Nutrition; Public Health

SUGGESTIONS FOR CONDUCTING GROWTH STUDIES. ERNEST H. WATSON and ROBERT C. MOEHLIG, Endocrinology **27**:411 (Sept.) 1940.

This is a discussion of the various factors which may be responsible for abnormalities of growth in children. The value of history, body measurements, roentgenograms, endocrine investigation, etc., in arriving at a diagnosis is pointed out. There are excellent photographs of the more common endocrine types. (An unfortunate choice is the one illustrating cretinism, the child having a suspiciously mongoloid facies.)

JACOBSEN, Buffalo.

HYGIENE OF INFANTS AND CHILDREN. RICHARD M. SMITH, J. Michigan M. Soc. **39**:391 (June) 1940.

The author presents a discussion of the various factors which influence health, together with some views on growth, development and periodic examinations. These factors are discussed under the headings of food, routines, habits, care of the body, environments, emotional adjustments and disease.

The author points out the change in content of medical practice and states: "The physician of the future will devote less time to curative medicine and more to prevention."

CAREY, Detroit.

CAMP SANITATION. C. A. HOLMQUIST, New York State J. Med. **40**:341 (March 1) 1940.

There are approximately 3,000 camps in the state of New York, occupied by from 2,000,000 to 3,000,000 persons a year. A large portion of these are in the Catskill and Adirondack mountains, many remote from villages and from medical facilities. Holmquist gives a review of the present sanitary code relating to such camps. The state department of health places the responsibility for the inspection of camps on the local health officers. It is required that a licensed physician be on call at all times and that a registered nurse be employed in larger camps.

AIKMAN, Rochester, N. Y.

THE FUNCTION OF A CHILD GUIDANCE CLINIC. HARRY A. STECKEL, New York State J. Med. **40**:364 (March 1) 1940.

The development and functions of a child guidance clinic are described.

AIKMAN, Rochester, N. Y.

Prematurity and Congenital Deformities

THE IMMATURE INFANT: STATISTICS FOR THE TEN YEAR PERIOD, 1929 TO 1938, IN THE PROVINCIAL INSTITUTE FOR YOUNG INFANTS. F. PINTO, Lattante **10**:242 (June) 1939.

In round numbers, there were 1,000,000 live births in Italy in 1936; 110,000 infants (11 per cent) died in the first year of life and 55,000 in the first month. There are 100,000 immature infants born each year, 40,000 dying in the first five days of life. The immature infant, therefore, accounts for a large part of the country's infant death rate.

Pinto's statistics show that of 1,607 infants entering his institution during ten years, 241, or 15 per cent, were immature; this incidence is about 5 per cent higher than that for the infant population as a whole. Of the 241, 95 (39 per cent) died during the first year of life. The mortality rate was higher for the immature infants under 2,000 Gm. in weight (62 per cent) than for those weighing 2,000 to 2,500 Gm. (30 per cent).

In answer to the question "What shall we do for the immature?", Pinto suggests: (1) well equipped facilities in the institutes for infants and in the

pediatric clinics; (2) a room for immature infants in all maternity clinics under the direction of a pediatrician; (3) formation of a nucleus of nurses specially trained to care for the immature infant, and (4) a requirement that midwives report by telephone the births of immature infants so that immediate assistance by trained workers may be made available.

HIGGINS, Boston.

NEW AIR-CONDITIONED ROOMS FOR PREMATURE INFANTS. F. CISLAGHI, Med. ital. **20**:301 (June) 1939.

Diagrams and schematic drawings of the two air-conditioned rooms for premature infants as set up in the two university clinics of Milan are presented. One room was set up in the obstetric clinic and the other in the pediatric clinic.

MARTOCCIO, Utica, N. Y.

A CASE OF SPINA BIFIDA WITH MULTIPLE MALFORMATIONS. F. CISLAGHI, Med. ital. **21**:116 (March) 1940.

The author describes the case of a premature infant with spina bifida (myelomeningocele) in the lumbar region, with accompanying malformations. These were hydrocephalus, severe lumbar kyphosis, shortening of the lower limbs with flaccid paralysis and bilateral equinovarus. The author feels that kyphosis such as occurred in this case is rare. The hydrocephalus was present at birth. Roentgenograms and autopsy observations are given. The etiology of spina bifida is discussed.

MARTOCCIO, Utica, N. Y.

SIRENOMELIA. GEORGE ILBERG, Ztschr. f. Geburtsh. u. Gynäk. **119**:95 (May) 1939.

A typical case of sirenomelia is described. Only one iliac and one umbilical artery were present; the large intestine was very short; the rectum, kidneys, ureters and ischial bones were absent; one femur and two tibias were present, but both fibulas were missing.

About 200 cases have been previously reported.

ADAIR and POTTER, Chicago.

CONGENITAL DEXTROCARDIA WITH COMPLETE TRANSPOSITION OF VISCERA—REPORT OF A CASE. T. F. SU and C. E. NIEH, Chinese M. J. **55**:276 (March) 1939.

A refugee girl 8 years of age was brought into the hospital because of dysentery. Physical examination revealed the point of maximum impulse of the heart to be in the fifth intercostal space on the right. There were no pathologic signs. The spleen and liver were not palpable. A roentgenogram taken during convalescence revealed transposition of the abdominal organs also.

NEFF, Kansas City, Mo.

FETAL DEATH DUE TO A SMALL DOSE OF QUININE. T. KUBOTA, Jap. J. Obst. & Gynec. **22**:128 (March) 1939.

The author reports a single case in which a slightly macerated fetus was delivered after 0.39 Gm. of quinine hydrochloride had been given the mother to relieve the pains. From this he concludes that quinine is highly toxic to fetuses and should not be administered to a pregnant woman.

ADAIR and POTTER, Chicago.

A CASE OF GARGOYLISM. M. L. JACOBI and P. J. WAARDENBURG, Maandschr. v. kindergeneesk. **9**:175 (Feb.) 1940.

The authors present a description of a case of gargoylism in a girl 5 years old who showed all the characteristic symptoms of the disease; some ocular symptoms were also present, and the fact is stressed that the parents were first cousins.

VAN CREVELD, Amsterdam, Netherlands.

DISTURBANCES IN FETAL DEVELOPMENT CAUSED BY AMNIOTIC CORDS. R. J. HARRENSTEIN, Maandschr. v. kindergeneesk. **9**:231 (March) 1940.

A description and a photograph are given of a fetus measuring 16 cm., with disturbances in the development of the extremities, caused by amniotic cords. The author discusses the origin of the amniotic cords, and on the changes seen in the fetus he founds his conclusion that these malformations are exclusively the consequence of the activity of the amniotic cords.

VAN CREVELD, Amsterdam, Netherlands.

Newborn

CARE OF THE SKIN IN THE NEW BORN INFANT. R. I. KLEIN and P. L. AIRES, Illinois M. J. **77**:337 (April) 1940.

A large part of the care which the newborn infant receives in a hospital is concerned with the prevention and treatment of cutaneous irritations and infections. The nonspecific neonatal dermatitis is the type more commonly encountered, i. e., the simple infantile dermatitis and the pustular dermatitis.

Although not bathing the skin of the newborn infant may not by itself reduce the incidence of impetigo, it is the preferable procedure, because the skin is handled less.

Aseptic technic and proper procedures both in the nursery and in the maternity division, plus prompt adequate isolation are most important in lowering the incidence of pustular dermatitis and decreasing the number and severity of the epidemics of this condition.

Keeping the baby away from infection, and keeping infection away from the baby are paramount.

BARBOUR, Peoria, Ill.

EFFECTS OF OBSTETRIC ANALGESIA ON THE NEWBORN INFANT. J. KOTZ and M. S. KAUFMAN, J. A. M. A. **113**:2035 (Dec. 2) 1939.

Comparing 800 babies whose mothers received paraldehyde during labor, 100 whose mothers were treated with pentobarbital sodium, 100 whose mothers were treated with pentobarbital sodium using the McCormick technic, and 100 controls, the authors found no change in the mortality rate, initial loss of weight, average temperature, pulse or respiration. The initial respiration was delayed with paraldehyde anesthesia from nine and eight-tenths seconds (in the control) to thirty-nine and one-half seconds.

No residual changes were found as a result of an injury at birth except in 1 case of Erb's paralysis. The babies of mothers who were treated with the drugs named were more drowsy on their first day.

HEERSMA, Kalamazoo, Mich.

ETIOLOGIC FACTORS IN NEONATAL ASPHYXIA. W. C. C. COLE, D. C. KIMBALL and L. E. DANIELS, J. A. M. A. **113**:2038 (Dec. 2) 1939.

Factors which may produce neonatal asphyxia were studied from the records of 5,000 mothers and babies. The authors include the work that has been offered to show the relation between fetal anoxia and cerebral injury. While more than one factor may be involved, in order of importance they are, prematurity, trauma of normal labor or labor involving dystocia or operative delivery, sedatives in proportion to the amount given, and the anesthetic in proportion to the time given.

HEERSMA, Kalamazoo, Mich.

ICTERUS GRAVIS NEONATORUM. R. A. STRONG and H. P. MARKS, J. Pediat. **15**:658 (Nov.) 1939.

Three cases of icterus gravis neonatorum are reported. Two of the infants were white, and one was a Negro. Autopsies on 2 of the infants are presented.

The third infant recovered. In addition to the 3 case reports, Strong gives a full discussion of the hematologic characteristics of the newborn infant, the causes of the disease, the pathologic changes, the clinical features, the differential diagnosis and the treatment and prognosis.

RAUH, Cincinnati.

VARIATIONS IN THE CONCENTRATION OF ASCORBIC ACID IN THE PLASMA OF THE NEWBORN INFANT. R. L. MINDLIN, J. Pediat. **16**:275 (March) 1940.

The course of the plasma ascorbic acid concentration in a series of newborn infants under different conditions of ascorbic acid intake is reported. The concentration of ascorbic acid in the plasma of the newborn infant was in every instance found to be higher than that in the plasma of the mother. The averages were 1.16 and 0.42 mg. per hundred cubic centimeters, respectively. Within twenty-four hours after birth the infants showed a marked drop in the concentration, and in the breast-fed infants this decrease continued to the end of the first seventy-two hours. At this time lactation is usually established, and the subsequent course of the ascorbic acid content of the plasma of these infants depended on the diet. In breast-fed infants breast milk high in ascorbic acid content caused an increase in plasma ascorbic acid. In artificially fed infants plasma ascorbic acid was found to be low during the first two weeks of life. Lactating mothers fed large quantities of ascorbic acid produced breast milk with a high concentration of ascorbic acid.

RAUH, Cincinnati.

NEUROLOGIC SEQUELAE OF PARANATAL ASPHYXIA. F. SCHREIBER, J. Pediat. **16**: 297 (March) 1940.

In a group of 900 children referred for neurologic examination, whose brain defects were thought to be related to conditions at birth, 70 per cent of those for whom reliable data on birth were obtainable were found to have a history of asphyxia, regardless of the manner of delivery or of whether the baby was full term, premature or a twin. Careful examination of the paranatal records disclosed a definite relation between fetal oxygen want and the later neurologic defect. Schreiber classifies the different mechanisms by which the infant brain may be deprived of oxygen, with resultant cell necrosis and later evidence of cerebral dysfunction, as follows: anoxic, anemic, stagnant and histotoxic anoxia. In anoxic anoxia the arterial blood is insufficiently saturated with oxygen. Aspiration of mucus, an excessive amount of amniotic fluid in the lungs or an enlarged thymus may produce this type of anoxia. In anemic anoxia the oxygen capacity of the blood is abnormally low. Stagnant anoxia is caused by a less than normal quantity of circulating blood. Failure of the heart to maintain an adequate circulation, low blood pressure in the mother, excessive pressure applied to the fetal head in marked dystocia or by the forceps are examples of causes of this type of anoxia. Histotoxic anoxia occurs when the oxygen supply is normal in all respects but the tissue cells are affected in such a manner that they cannot use the oxygen properly. The biochemical reactions of these cells may be altered by drugs, anesthetics or poisonous substances acting directly on neuronal tissue. Schreiber believes that foremost among the factors inducing asphyxia are the drugs and anesthetic agents used to produce analgesia and amnesia in the mother. The asphyxia resulting from excessive use of drugs to produce unconscious labor is no less serious in its effect on the baby than that from any other cause. Any method of delivery which produces a defective infant has no compensation for the mother, child or physician.

RAUH, Cincinnati.

HEART MURMURS IN NEWBORN INFANTS. R. A. LYON, L. W. RAUH and J. W. STIRLING, J. Pediat. **16**:310 (March) 1940.

Heart murmurs were detected in 147 (1.9 per cent) of 7,673 newborn infants examined during the first week of life. Murmurs were more frequent in Negro

than in white infants. Of the group of 147 infants with murmurs, 92 were followed later in life. Four had died, and on 2 autopsy was performed and heart disease found. Fourteen had persistent systolic murmurs which were considered to represent some form of congenital cardiac lesion. Of the 74 remaining patients, 71 were entirely well, without any clinical evidence of heart disease, and 3 had functional murmurs or extrasystoles.

RAUH, Cincinnati. [FROM AUTHORS' SUMMARY]

PNEUMONIA IN THE NEW-BORN. A. R. MACGREGOR, Arch. Dis. Childhood **14**:323 (Dec.) 1939.

Pathologic examinations were made of 541 consecutive infants aged up to 28 days who came to autopsy. Inflammatory changes were encountered in the lungs of 177. The pathologic study of the 177 cases of pneumonia revealed that they could be divided according to their outstanding pathologic characters into four distinct groups, thus: (1) pneumonia associated with aspiration of contents of the amniotic sac or vagina (*a*) in the deadborn (11 cases) and (*b*) in the liveborn (33 cases); (2) pneumonia associated with other pulmonary conditions due to stress of birth or other difficulty peculiar to the newborn, as atelectasis, hemorrhage (33 cases); (3) bronchopneumonia and allied types (82 cases); (4) septicemia with secondary involvement of the lungs (18 cases). The pathologic character and genesis of the types of pneumonia that occur in the deadborn and in those who die in the first few days of life are discussed. The importance of asphyxia as a factor in the production of these types of pneumonia is emphasized.

KELLY, Milwaukee.

SYPHILITIC ICTERUS IN THE NEWBORN. H. SLOBOZIANU and V. T. IONESCU, Rev. franç. de pédiat. **15**:261, 1939.

The literature on syphilitic icterus of the newborn is reviewed, and 2 cases are reported. The first was characterized by rapidly progressing icterus, enlargement of the liver and spleen, hematuria and anemia of the pseudoleukemic type. Autopsy showed fatty cirrhosis of the liver, atrophy of the germinal centers of the spleen, hyperemia of the glomeruli of the kidney with degeneration of the tubercles, and atrophy of the adrenal cortex with hemorrhage into the medulla. The second infant showed a retention type of jaundice for eighteen days. The liver and spleen were enlarged. The Wassermann and Kahn tests were positive. Clinical improvement occurred coincidentally with antisyphilitic treatment.

LESLIE, Evanston, Ill.

INVESTIGATIONS ON THE TRANSMISSION OF BACILLUS BIFIDUS TO THE NEWBORN. W. MAASSEN and W. ALBERTSEN, Arch. f. Hyg. **123**:367 (March 10) 1940.

Maassen and Albertsen undertook to ascertain the source of Bacillus bifidus found in the intestines of the newborn, and its ordinary way of entrance. They were not able to culture B. bifidus from the vaginal flora of the mother, from her milk or from the neighborhood of her nipples, but were able to do so from the stools in almost 100 per cent of the cases. In several instances the bath water of the newborn was found positive for this organism but only after delivery through the birth canal, not after cesarean section.

The authors conclude that the intestinal contents of the mother are the main source of B. bifidus. The transmission takes place either directly during delivery or indirectly by way of the bath water, nursing personnel or the hands of the mother. It appears in the newborn infant's stool not earlier than forty-eight hours after delivery. The mouth seems to be the main path of invasion.

FALKENHEIM, Rochester, N. Y.

Acute Contagious Diseases

A Subclinical Endocrinology as a Factor in Autarceologic Susceptibility to Poliomyelitis. W. Lloyd Aycock, Endocrinology **27**:49 (July) 1940.

There is epidemiologic evidence that the virus of poliomyelitis is widespread but that the occurrence of the paralytic disease in those exposed to the virus is limited and selective. Familial tendency, seasonal and geographic factors and pregnancy all may play a part in determining the persons affected. Particularly association of poliomyelitis with a certain constitutional type, "juvenile adiposo-genital hypopituitarism," suggests that endocrine dysfunction may play a part.

Experimentally injection of estrogenic substance into castrate immature female monkeys enhanced resistance to intranasal instillation of the virus. Also, patients with poliomyelitis were found to excrete more estrogenic substance than did normal controls. These observations suggest that autarcesiologic susceptibility to poliomyelitis may lie in some fault in the economy of estrogenic substance.

Jacobsen, Buffalo.

The Mechanical Respirator in Poliomyelitis. James L. Wilson, J. Pediat. **16**:462 (April) 1940.

Wilson believes that confusion exists about the selection of patients with poliomyelitis for treatment in a respirator and that there is a misconception as to the purpose of respirator treatment. The respirator will aid only when there is paralysis of the intercostal muscles or of the diaphragm or in rare instances in which there is hypofunction (not dysfunction) of the respiratory centers. Unfortunately most physicians think of the respirator only as a machine for life saving and for aiding breathing until enough recovery occurs to enable the patient to carry on by himself. The respirator should be considered a device for providing physiologic rest for the muscles of respiration. Too frequently use of the respirator is delayed too long or the patients are taken out of the machine too soon. Two new types of respirator are described. One, a room-sized respirator, is able to care for several patients at one time and has given excellent results. The second type is now being developed. It consists of a rigid or semirigid jacket to be put on the chest and abdomen, making an air-tight space over the body. The intermittent evacuation of this space by means of hand-driven or motor-driven pumps causes respiration to be induced by the same principle as in the Drinker respirator. Wilson suggests that a national coordinated program for the handling of respiratory paralysis associated with poliomyelitis be planned so that the burden of local outbreaks may be spread over other communities and the expensive machines used over wider areas.

Rauh, Cincinnati.

Sulfanilamide in the Treatment of Scarlet Fever. A. Clement Silverman, New York State J. Med. **40**:317 (March 1) 1940.

It is difficult to estimate the results obtained with sulfanilamide in the treatment of scarlet fever because of the striking change that has taken place in the character of scarlet fever. The mortality in 1938 was 0.01 of that in 1861. Silverman found that sulfanilamide had no effect on the eruption and toxic manifestations but that it reduced the incidence of complications, especially otitis media. Sulfanilamide does not displace antistreptococcus serum for toxemic conditions; for those, combined treatment should be used.

Aikman, Rochester, N. Y.

The Control of Contagious Disease in the Pediatric Wards of a General Hospital. Carl C. Fischer, Pennsylvania M. J. **43**:1457 (July) 1940.

These data, covering a two year study of the results of a plan for control of contagious disease in the pediatric wards of a general hospital, show that the abolition of the usual formal quarantine greatly increased the bed capacity of the

ward without apparently increasing the number of primary and secondary contagious conditions; that the routine use of immune globulin (human) as a means of prevention was accompanied with only a small percentage of mild local reactions, and that the statistical data made available by a complete history of infections and immunizations yield some interesting material suggesting the trends of infections and of immunity which may be applied to some of the practical problems of control of contagious disease.

LOGUE, Williamsport, Pa.

THE GEOGRAPHIC DISTRIBUTION OF DISEASE: III. A DECADE OF POLIOMYELITIS IN LOUISIANA. ALBERT E. CASEY and BRANCH J. AYMOND, Pub. Health Rep. **55**:1295 (July 19) 1940.

This is a study of 676 cases of poliomyelitis for the decade ending in January 1939. While the incidence was widely distributed, the preponderance was in small towns. There was some evidence that the incidence was influenced by the disposal of sewage. In 64 communities with no water supply or arrangements for sewage disposal the incidence was 39.7 cases per 100,000 of population; in 27 with water supply and sewage disposal the incidence was 26.6, and in 87 with water supply but no sewage disposal it was 83.6.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **55**:1371 (Aug. 2) 1940.

For the period from June 16 to July 13, influenza was the only disease above the median prevalence, and this only slightly. All other diseases reportable were below the median; poliomyelitis, for example, was only 75 per cent of the average. The total mortality from all causes was 10.2 per 1,000, also below the average.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **55**:1933 (Oct. 25) 1940.

Poliomyelitis for the period of September 8 to October 5, with 2,859 cases reported, was above the median incidence. It was most prevalent in the North Central and South Atlantic regions. Influenza was increased 20 per cent, particularly in the South Central and the mountain regions. Measles was also above the median incidence, being increased in all regions. The average mortality from all causes was 10.6 per 1,000, which is 0.3 above the average.

SANFORD, Chicago.

MODERN CLINICAL METHODS TO COMBAT WHOOPING COUGH INFECTION. S. W. WILLIAMS, M. J. Australia **1**:690 (May 18) 1940.

Experimenting with pertussis vaccine of various strengths for cutaneous testing, Williams found that a vaccine containing 1,000,000,000 organisms per cubic centimeter gives reliable results. A positive response to the test develops during the course of the disease, and there is a correlation between a history of whooping cough and a positive response to the cutaneous test. Following the intradermal injection of 0.1 cc. of such a vaccine into a sensitized subject, a positive reaction develops in sixteen hours, remains for eight to twelve hours, fades and disappears in forty-eight hours and leaves a pigmented area in the skin. Few positive reactions are obtained with more dilute suspensions, while stronger suspensions produce a nonspecific inflammatory response regardless of the immune state of the patient. In the course of active immunization of infants approximately 10 per cent had a troublesome but not dangerous reaction to the injections. Passive immunization early in the course of the disease was attempted by the intramuscular injec-

tion of 30 cc. of parent's blood. Of 15 patients so treated the disease was mild in 13 and severe in 2, whereas of 42 controls the disease was mild in 20, severe in 18 and complicated by pneumonia in 4.

GONCE, Madison, Wis.

CEREBRO-SPINAL MENINGITIS. W. L. CALOV, M. J. Australia **2**:51 (July 20) 1940.

This is a good general discussion of meningococcic meningitis presented in textbook form.

GONCE, Madison, Wis.

AN OUTBREAK OF CEREBRO-SPINAL MENINGITIS IN A FOUNDLING HOSPITAL: THE TREATMENT OF CARRIERS WITH "M & B 693." J. F. MEEHAN and C. R. MERRILLEES, M. J. Australia **2**:84 (July 27) 1940.

Of three hundred children accommodated, 30, all associated with one unit of the institution, were affected with cerebrospinal meningitis between November 1937 and March 1939. General hygienic measures and local applications failed to prevent spread of the disease. Bacteriologic examinations of swabs disclosed 75 carriers, mostly in the affected wards. The carrier children were treated with sulfanilamide for two periods of five days each with an interval of five days between. The daily dose used was 1½ grains (0.09 Gm.) per pound of body weight on the first day and 1 grain (0.06 Gm.) per pound thereafter. This treatment was followed by an immediate drop in the number of carriers from 75 to 6 after one course, to 4 after two courses and to 3 after three courses.

GONCE, Madison, Wis.

INFECTIOUS DISEASES IN 1940. C. DOPTER, Paris méd. **1**:265 (June 1-8) 1940.

This is a review of the recent literature on infectious diseases.

LESLIE, Evanston, Ill.

GENERALIZED POLYRADICULONEURITIS AFTER MUMPS, SCARLET FEVER AND CHICKENPOX. JEAN CATHALA, Paris méd. **1**:279 (June 1-8) 1940.

In the first case reported the condition occurred on the eighth day after the onset of mumps associated with orchitis. Muscular weakness and vague pains characterized the onset. This was followed by incomplete quadraplegia and double facial paralysis and finally by paralysis of the respiratory mechanism and death. The spinal fluid was xanthochromic; it contained a large amount of albumin and a normal number of cells. The central nervous system showed no abnormality. Unfortunately, the peripheral nerves were not examined. Four other cases are cited in which death occurred from respiratory failure. The respiratory paralysis was not the consequence of a bulbar lesion but was probably due to lesions of the phrenic and the dorsal-cervical nerves.

If no marked respiratory paralysis occurs, eventual complete recovery is the rule. The author's other 2 cases belong in this category. No new light is shed on the cause of the disease.

LESLIE, Evanston, Ill.

THE TREATMENT OF MENINGOCOCCUS MENINGITIS WITH SULFANILAMIDE EXCLUSIVELY. A. RUSESCO, V. VOICULESCO and A. DIACONU, Presse méd. **48**:471 (May 8-11) 1940.

The authors review the experimental and clinical facts in the treatment of meningococcus meningitis. From these facts and from personal observations in 10 cases they conclude that administration of sulfanilamide is the best method of treatment, with the fewest complications. Serum should be administered to patients who are refractory to sulfanilamide. In the cases presented the drug was administered intramuscularly and intrathecally during the acute stages. Some convalescent patients received sulfanilamide by mouth. Only in 1 case was the drug given by mouth during the acute stage. There were 9 recoveries.

DAFFINEE, Boston.

DIPHTHERITIC CROUP. F. TECILAZIC, Med. ital. **21**:28 (Jan.) 1940.

The author reviews 975 cases of croup observed in the hospital from 1932 to 1938. The morbidity curve of diphtheritic croup follows closely that of diphtheria in general. In the last fifteen years there has been an increase in the number of cases of croup. Croup is most prevalent and carries its greatest mortality from January to May. More boys than girls are affected, and this predilection is most evident in boys of school age. The age group from 2 to 4 years was most frequently affected.

MARTOCCIO, Utica, N. Y.

POTASSIUM CHLORATE IN THE TREATMENT OF ACUTE ANTERIOR POLIOMYELITIS. A. MACCHI and M. SACCA, Med. ital. **21**:105 (March) 1940.

Forty infants and children were treated with potassium chlorate. The dose was 10 centigrams per kilogram of body weight, divided into twelve doses and given every two hours. Three to 5 drops of a 3 per cent solution was instilled into each nostril twice a day. No improvement in the course of the disease was noted.

MARTOCCIO, Utica, N. Y.

ABILITY OF TETANUS TOXIN TO IMMUNIZE AGAINST DIPHTHERIA TOXIN. A. GALEOTTI FLORI and M. CECIONI, Riv. di clin. pediat. **38**:353 (June) 1940.

Guinea pigs receiving immunity by large doses of tetanus anatoxin also have some immunity to diphtheria toxin. A negative reaction to the Schick test and survival after injections of a minimum lethal dose of diphtheria toxin have been observed.

Observations on children did not reveal a practical degree of immunity, as the Schick reaction remained positive after the giving of tetanus anatoxin.

In guinea pigs, vaccination with diphtheria anatoxin did not produce any immunity to tetanus toxin.

HIGGINS, Boston.

DIPHTHERITIC CROUP IN INFANCY. M. H. BORTAGARAY, An. Soc. puericult. Buenos Aires **6**:1 (Jan.-March) 1940.

During 1939 there were 56 cases of diphtheria, in which 7 patients had croup and 3 showed signs of suffocation. The author gives the symptoms and the diagnostic procedures and then outlines thoroughly the treatment.

HERRON, Oak Ridge, La.

MENINGOENCEPHALITIS IN MEASLES. A. INVALDI and M. D. URIARTE, Rev. Soc. pediat. de Rosario **4**:171, 1939.

It is interesting that the authors date the recognition of the neurologic complications of measles to the year 1724, when Nebel studied a patient with ocular paralysis occurring during the course of the disease. The first autopsy in a case of measles encephalitis was done in 1868 by Bergeron. In the present communication the authors report in detail the histories of 7 patients with neurologic complications; the cases were observed among 253 cases of measles. The variety of neurologic manifestations possible and the lack of correlation with the severity of the measles are discussed.

DIETRICH, Beverly Hills, Calif.

HEINE-MEDIN MENINGITIS. C. M. MORRA, Rev. Soc. pediat. de Rosario **4**:187, 1939.

A case of a condition which was presumably nonparalytic poliomyelitis in a 22 month old infant is reported.

DIETRICH, Beverly Hills, Calif.

DIPHTHERITIC BALANITIS. E. G. RAUSCHER, München. med. Wchnschr. **87**:537 (May 17) 1940.

Diphtheritic involvement of the penis is rare. Rauscher reports the case of a boy admitted to the hospital for measles, from which he made an uneventful recovery. A month after the onset of his measles he had fever and complained of dysuria. The penis and the scrotum were edematous, and there were several areas covered with a light yellow exudate. Virulent diphtheria bacilli were cultured from these areas. Treatment consisted of the injection of 6,000 units of diphtheria antitoxin and local applications. Several days later an additional dose of 10,000 units of antitoxin was administered, although the infection was improving. After the first week compresses of diphtheria serum were applied locally. Recovery was complete.

No mention was made of nose or throat cultures from the patient or other children in the ward.

BRAHDY, Mount Vernon, N. Y.

SMALLPOX VACCINATION TECHNIC. A. GROTH, München. med. Wchnschr. **87**:650 (June 14) 1940.

In reply to a question concerning methods for vaccination against smallpox Groth states that the only legally accepted method is the cutaneous scratch technic. It is advised to make two scratches 3 mm. long and to apply a vaccine which is not diluted by the addition of water or glycerin.

BRAHDY, Mount Vernon, N. Y.

CONSIDERABLE CONDUCTION DISTURBANCE OF THE HEART IN A CHILD AS AN EXPRESSION OF PERMANENT DAMAGE CAUSED BY DIPHTHERIA. E. STEPHAN, Ztschr. f. Kinderh. **61**:297 (Oct. 5) 1939.

A 9½ year old girl had apparently had diphtheria three and one-half years prior to her examination by Stephan. Electrocardiographic curves are presented showing a disturbance in conduction.

SIEMSEN, Chicago.

CHANGES IN ANTITOXIN TITER WITH PROPHYLACTIC DIPHTHERIA INOCULATION. O. ERUST and F. ALLIN, Ztschr. f. Kinderh. **61**:351 (Oct. 5) 1939.

In agreement with other authors, Erust and Allin found that in practically all instances of injection of anatoxin or alum-precipitated toxoid the injection was followed by a temporary reduction in antitoxin titer (negative phase) lasting about six days. Whether the negative phase is of importance clinically (increased susceptibility) is uncertain. Some authors have reported an immediate rise in antitoxin titer.

SIEMSEN, Chicago.

THE CONTROL OF SCARLET FEVER: II. ACTIVE AND PASSIVE IMMUNIZATION AGAINST SCARLET FEVER. P. L. FAN, Chinese M. J. **56**:532 (Dec.) 1939.

In an earlier number of the *Chinese Medical Journal* [**51**:859 (June) 1937] the author reported on the findings from Dick tests in a large number of persons of various ages in China. In the present report he attempts to answer the question as to whether the spread of scarlet fever can be prevented and children thereby protected.

Following the epidemic of scarlet fever in the Tsinan area in 1936, when the Dick test had been done in a large series, the author was interested in following up those who had been given the test before the epidemic. Of 1,435 negative reactors, 0.7 per cent contracted scarlet fever, with no deaths; of 580 positive reactors, 4.8 per cent contracted the disease within one to twelve months after the tests had been performed; the deaths from scarlet fever in this group were 8. Kolmer is quoted as believing that a spontaneous negative reaction is more durable than a

negative reaction following artificial immunization. The author concludes that there are only a few cases in which the Dick test does not indicate the immunity of the subject to scarlet fever. Passive immunization by means of injections of the blood of persons convalescent from scarlet fever or immune protects the subject for two or three weeks and is useful if continuous contact with a patient is unavoidable. Scarlet fever toxoid had definite effect in the control of an epidemic in Tsinan.

NEFF, Kansas City, Mo.

OSTEOMYELITIS VARIOLOSA—REPORT OF A CASE. P. L. FAN, Chinese M. J. **57**:571 (June) 1940.

Osteomyelitis from smallpox is not extremely rare. The author observed 3 cases during six months. A detailed report concerns a child of 19 months who had the disease sixteen days prior to swelling of the right elbow, due to a marked periostitis of the lower end of the humerus and, later, the distal portion of the radius. Healing progressed to a complete cure.

NEFF, Kansas City, Mo.

PATHOGENESIS OF ENCEPHALITIS POSTVACCINALIS. J. D. VERLINDE, Maandschr. v. kindergeneesk. **9**:368 (June) 1940.

It is possible to produce a postinfection encephalitis in the course of Carré's disease in dogs by contaminating them with the virus of the disease during guanidine intoxication. The same result is obtained in dogs by vaccinating them against smallpox during guanidine intoxication. With rabbits, calves and monkeys the experiments did not succeed. Probably in these animals and perhaps also in man another form of autointoxication from the intestinal tract plays an etiologic role in postvaccinal encephalitis. Several strains of dermovaccine, but especially strains of neurovaccine, were found to have encephalitogenic properties. Preventive and curative measures should be directed against predisposing metabolic factors.

VAN CREVELD, Amsterdam, Netherlands.

DEVELOPMENT OF THE EXANTHEM IN MEASLES. J. MUNK, Maandschr. v. kindergeneesk. **9**:385 (July) 1940.

Munk presents a discussion of the rhythm in which the measles exanthem appears and disappears. The author is of the opinion that in this process the skin plays an active part (esophylactic, according to Hoffmann) in the formation of antisubstances.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

RHEUMATIC FEVER—DIAGNOSIS AND TREATMENT. HUGH MCCULLOCH, J. Michigan M. Soc. **39**:243 (April) 1940.

The author classifies measures used in the treatment of rheumatism and heart disease into two groups: first, specific measures to control the streptococcus infection and, second, measures used in control of the process through secondary factors which are known to modify the disease in its effect on the patient.

For the first group the author states that sulfonamide is of no value and limits his discussion to the second, which includes such factors as heredity, social status, climate, age of patient and type and number of attacks. He classifies rheumatic patients into three groups representing the varying course of the disease: rheumatic fever without heart disease, rheumatic heart disease without circulatory failure and circulatory failure. Treatment is discussed for each of these three groups.

CAREY, Detroit.

ROCKY MOUNTAIN SPOTTED FEVER IN CHILDREN. DAVID W. MARTIN, J. Pediat. **16**:468 (April) 1940.

Martin reports 8 cases of Rocky Mountain spotted fever in which the patients ranged in age from 2 to 8 years. The disease is caused by one of the rickettsia bodies, Rickettsia ricketti, and transmitted by at least three species of ticks: Dermacentor andersoni, which transmits the severe western variety; Dermacentor variabilis, or dog tick, which transmits the moderate to severe eastern disease, and the rabbit tick. The life cycle of the tick is described. Five of the 8 patients gave a history of tick bite three to fourteen days prior to the onset of symptoms. Fever and rash are the characteristic symptoms. The rash is generalized; at first it is macular, gradually becoming papular, and in about a week it is petechial. The rash fades at the end of the second week, leaving a brownish discoloration until the end of the third. The complications most commonly encountered are bronchial pneumonia, phlebitis, hiccup and hemorrhages from the nose, intestine or kidneys. The most commonly used laboratory aid to diagnosis is the Felix-Weil reaction. Agglutination of Bacillus proteus (X_2 and X_{19}) by the patient's serum in titers above 1:160 is considered diagnostic. The treatment is purely symptomatic. There were no deaths in this series of 8 cases. A vaccine has been prepared by the United States Public Health Service which protects against the disease for one year and reduces the mortality among those contracting the disease. The cost of this vaccine makes its widespread use impractical. Ticks should not be removed from dogs, and when ticks are removed from human beings a steady pull should be exerted to avoid crushing them.

RAUH, Cincinnati.

REPORT ON THE EPIDEMIOLOGY OF RHEUMATIC INFECTION IN SOUTH AUSTRALIA. M. J. Australia **1**:461 (April 6) 1940.

Rheumatic infection is a serious matter. The amount of crippling of the heart it produces makes it even more important than poliomyelitis with its crippling of limbs. Australia is fortunate in being less severely attacked than most countries; yet even there rheumatic infection and the associated heart disease exact a dreadful toll. To cure damage of the heart is not possible; to prevent damage from rheumatic infection is a public health problem worthy of the best effort. The committee's research has shown that the predisposing causes are essentially the same in Australia as elsewhere; poverty, damp living conditions and overcrowding play strong parts. Agreement as to the actual cause of juvenile rheumatism is yet to be reached. The streptococci are intimately concerned, but some features of the illness are difficult to explain on the basis of streptococcic infection alone. Whether an associated virus is present is one of the many problems awaiting solution. Some health authorities abroad have introduced compulsory notification of acute rheumatism, but with the types of disease often ill defined and the actual cause still unknown, compulsory notification is necessarily limited in its value. In the present state of knowledge the best method of dealing with cardiac crippling is to prevent it. The care of rheumatic patients in the acute phase of their illness and suitable management in convalescence are essential and require ample and good institutional facilities. The establishment of rheumatic supervisory centers in many cities has proved of great value. The suitable occupational training of young adults with damaged hearts must not be overlooked. Hospital schools and vocational training centers make possible some suitable and useful work during the long period of convalescence; neglect of this need may leave the patient a misfit for life. There is need for continued research into the prime causes of rheumatic infection. Continued attention to town planning, to sanitation and housing, to health education and to any means for enabling communities to live hygienically will achieve much. In trying to cope more effectively with rheumatic infection lies a duty and an opportunity for preventive medicine.

GONCE, Madison, Wis.

TETANUS SECONDARY TO A NASAL LESION. DONALD PATERSON, Proc. Roy. Soc. Med. **33**:373 (May) 1940.

A boy aged 2½ years was admitted to the hospital because he had suffered from convulsions for four days. On physical examination the only abnormality found was paralysis of the left facial nerve, and it was thought at the time that there must have been some cerebral damage at birth or a recent vascular lesion and that the fits were epileptic. Three days later the temperature began to rise, and next day well marked trismus was noticed. The child presented a typical picture of tetanus. He was treated with antitetanic serum and avertin with amylene hydrate and was fed through the nasal tube entirely. When the nasal tube was passed up the left naris it was found to be blocked with three lumps of coal as large as peas. The child recovered in just four weeks from the onset of the illness.

WILLIAMSON, New Orleans.

CLINICAL FORMS OF RHEUMATISM IN CHILDREN. LÉON BABONNEIX and RENÉ PRIEUR, Arch. de méd. d. enf. **43**:129 (May-June) 1940.

Among the disorders of childhood and adolescence, rheumatism assumes an importance even greater than that of cardiac disease; it impedes organic development, produces chronic invalidism and is a common cause of death. While the articular symptoms ordinarily predominate, these may be minimal or entirely absent. Grenet has called special attention to extra-articular invasions.

The authors discuss the disease under these classifications. In considering the first type, the usual symptoms of rheumatic polyarthritis are reviewed in a large series of cases, together with an extended description of those in which there occurred grave complications, such as pericarditis, pancarditis, pleurisy, pulmonary congestion, edema and other visceral accidents.

In the second category are listed the so-called pure infectious forms described first by Trousseau, of which the typhoid type is perhaps the best example, and the visceral forms, with which the brunt of the infection is found in the heart, the respiratory apparatus or the nervous system.

AMESSE, Denver.

SALMONELLA SEPTICEMIA AND BACTEREMIA IN INFANTS. A. R. GUERRA, E. PELUFFO, M. LAGUARDA and P. L. ALEPPO, Arch. de pediat. d. Uruguay **10**: 669 (Nov.) 1939.

In examining 141 infants ranging in age from 18 to 21 months, the authors found 14 cases of Salmonella infection. The blood of 6 of the cases showed colon bacilli, 6 showed Salmonella and 2 showed the bacilli of Shiga dysentery. The blood picture in the older children was generally normal.

The authors point out that manifestations of typhoid in the older child are generally confined to the intestinal tract and appear as intestinal diarrhea. In the younger child this infection often presents the picture of generalized sepsis, with a positive blood culture.

The authors believe that salmonellosis is a fairly common manifestation in the infant when no typhoid or paratyphoid can be demonstrated. The salmonellosis becomes more rare in the older child and paratyphoid, A or B, more common.

SCHLUTZ, Chicago.

CHAGAS' DISEASE. G. GASIC, Rev. chilena de pediat. **10**:31 (Jan.) 1939.

The author reports a case of Chagas' disease. This is the first case of this rare disease ever reported in Chile. The condition occurred in a child which had never left its small village and had been in a home infested with bedbugs.

Trypanosoma cruzi, the infectious agent of Chagas' disease, was found in 50 per cent of the bedbugs which the author examined. Edema of the lids and conjunctival infection with general symptoms of malaise, anorexia and low grade fever were observed. There was adenopathy of the preauricular and submaxillary

glands. In the early stages of the disease the parasite could not be demonstrated in the blood.

The great edema of the lids was the most marked and persistent symptom. The blood showed a 75 per cent increase of lymphocytes. Twenty five days after the onset of the disease T. cruzi was found in the blood. The organisms were numerous. Marked tachycardia and slight sinal arrhythmia developed. The patient made a complete recovery.

SCHLUTZ, Chicago.

INCIDENCE OF HEMOLYTIC STREPTOCOCCI IN THE THROATS OF HOSPITAL NURSES. A. E. TOWERS, H. WEI and H. YÜ, Chinese M. J. **57**:154 (Feb.) 1940.

This communication comes from the Lester Chinese Hospital and the Henry Lester Institute of Medical Research, Shanghai, China.

The survey indicates that there is always a high percentage (50 or above) of nurses who carry hemolytic streptococci. It becomes highest when there is an occurrence of scarlet fever among the nursing staff or of puerperal septicemia among the maternity patients.

NEFF, Kansas Gity, Mo.

TWO CASES OF HEAVY MANIFESTATION OF ASCARIS LUMBRICOIDES. H. F. HSÜ, Y. C. FAN, C. C. TAN and K. CH'IN, Chinese M. J. **57**:168 (Feb.) 1940.

One of these case reports is of interest because of the early symptoms resembling a surgical emergency, such as might happen in childhood.

At an operation for tentatively diagnosed intestinal perforation in a young woman, masses of living ascaris worms were found in the peritoneal cavity and some in the intestinal lumen. Additional worms escaped from the wound for two days after the operation and were collected on the dressings. The patient's eosinophil count was 0.2 per cent. Death occurred from pneumonia; autopsy revealed 418 ascaris worms in the omentum, subphrenic space, fallopian tubes, esophagus, stomach and intestines.

NEFF, Kansas City, Mo.

Chronic Infectious Diseases

PULMONARY TUBERCULOSIS IN THE SECOND DECADE OF LIFE: ITS DEVELOPMENT AND FATALITY. D. ZACKS, Am. Rev. Tuberc. **39**:683 (June) 1939.

If the value of case-finding surveys for the detection of early tuberculous infection is seriously questioned, the answer is clearly set forth in this paper. The insidious development of the disease during the second decade of life and the all but hopeless prognosis of late found tuberculosis would seem to make systematic efforts at early diagnosis almost mandatory. This study is based on the observation of 536 white children over periods ranging from one to twelve years—i. e., "a period of 2,144 person years, or an average of four person years" (a person year representing "the experience of one person who was observed for one year").

The disease in its chronic form always has an asymptomatic onset, its presence being revealed only by roentgen examination. Even during development and spread, no retardation in the patient's growth occurs. Cavities may develop without any objective or subjective symptoms. Serial roentgen examinations provide the only measure of the presence, extent and progress of the disease. A qualitative description of the lesions is not possible from roentgenograms alone, but serial roentgenograms give the really important information, such as whether the lesions are progressive or retrogressive. Early in the second decade of life, tuberculous disseminations or reinfections progress almost imperceptibly, and toxic symptoms or symptoms referable to the chest are not usually evident until the middle or toward the end of the pubertal period. At this stage any lesion which has been differentiated from nonspecific lesions should be regarded as of grave import. The retrogressive type of lesion tends to subside in time, and the patient may survive

puberty, the most critical period for this group of patients. Progressive lesions, on the other hand, will kill the great majority of patients within ten years. While the incidence of pulmonary tuberculosis is twice as high in girls of this age, the case fatality is essentially the same as in boys.

The development of the disease in this group at the end of four person years of observation is summarized as follows:

1. Two thirds of the patients have shown progressive changes by roentgen examination.

2. Of the patients with asymptomatic lesions, 44.5 per cent have aquired symptoms and signs of tuberculosis.

3. Of 65 boys and 127 girls who were still without symptoms, 33.8 and 41.7 per cent, respectively, showed progressive lesions.

4. Of the whole group, 19.3 per cent have cavities.

5. Of the whole group, 231 have begun to have sputum containing tubercle bacilli.

6. Ninety-five girls and 27 boys have died of pulmonary tuberculosis.

7. Of the boys, 74.5 per cent were treated in a sanatorium, compared with 68.3 per cent of the girls.

EUGENE H. SMITH, Ogden, Utah.

PULMONARY TUBERCULOSIS IN THE SECOND DECADE: ITS TREATMENT AND PROGNOSIS. D. ZACKS, Am. Rev. Tuberc. **39**:703 (June) 1939.

In this paper Zacks records his observations on a group of 536 children with pulmonary tuberculosis whose cases were followed for from one to twelve years, averaging four years per person. Many lesions formerly labeled as "latent," "inactive" or "healed," because of lack of symptoms and minimal roentgen findings, are found by means of serial roentgen investigation to be in reality "progressive." Treatment, however, yet lags behind "case-finding" in efficiency. Rest in bed alone does not modify the course or reduce the mortality of progressive lesions. The same is also true of advanced lesions treated by pneumothorax. The most that can be said for such treatment in cases of bilateral involvement is that it tends to prolong life. As to the efficacy of collapse therapy in early lesions, the answer will require five years more of observation. In some cases there is retrogression without treatment, and in others there is progress despite treatment.

Zacks's directions for treatment are as follows:

1. For patients of from 5 to 9 years, with chronic subclavicular infiltrations, use rest in bed alone.

2. In older patients, those with cavities and those with apical lesions beyond the second anterior ribs, institute collapse immediately.

3. For patients with subclavicular lesions, allow a month or two in bed for observation. If retrogressive changes do not occur, or if the lesions remain stationary or spread, attack at once. There are some exceptions to this rule in perihilar or peritracheal infiltrations.

4. If apical lesions are of not greater extent downward than the second anterior ribs, observe them over a period of three to six months. If there is no retrogression, attack by pneumothorax. If collapse alone is unsuccessful, surgical treatment of adhesions or thoracoplasty may become necessary.

The prognosis of soft early lesions during the second decade of life is uncertain for at least ten years. The most important prognostic indicator is the behavior of the lesions as determined by serial roentgen films. Lesions that progress, ultimately, do poorly; those that retrogress, on the whole, do well. Retrogressive lesions should be observed by serial films until definite stabilization is evident, either by calcification or strandlike fibrosis or both.

EUGENE H. SMITH, Ogden, Utah.

THE EPIDEMIOLOGICAL ASPECT OF THE NEGATIVE TUBERCULIN REACTION. M. PARETZKY, Am. Rev. Tuberc. **39**:754 (June) 1939.

To facilitate the study of patients whose reaction to tuberculin was negative, Paretzky classified them as follows: (1) patients possessing high specific immunity in the face of constant and prolonged exposure; (2) patients previously sensitive to tuberculin, with subsequent complete immunization; (3) patients with low immunity; (4) patients whose reaction to tuberculin subsequently became positive without their contracting the disease.

The first three groups only are considered in detail in this paper, with case reports and comments on possible epidemiologic factors involved.

While it is impossible to measure the amount of infection or the degree of immunity possessed by a patient, the development of disease is determined by these two factors. Immunity to be effective must be sustained. It may be lowered by intercurrent infections and may be broken down by frequent and regular exposure to infection. It may also vary in degree from time to time or become dormant. The amount of infection, its virulence and frequency, the intimacy and regularity of contact are also of paramount epidemiologic importance. To the author, however, it appears that successful resistance to tuberculosis depends a great deal more on the function of specific immunity than on the degree of exposure to infection.

EUGENE H. SMITH, Ogden, Utah.

DETECTION OF TUBERCULOSIS IN GROUP SURVEYS. P. T. KNIES, Am. Rev. Tuberc. **39**:766 (June) 1939.

A comparative study of two groups to determine the relative value of tuberculin tests and fluoroscopic examinations for the detection of tuberculous infection showed that an error approximating 25 per cent was possible when dependence was put on cutaneous reactions alone. Greater accuracy would be obtained by the combined use of both methods in clinical as well as in epidemiologic surveys under the conditions present in the experiment. As an agent for testing cutaneous sensitivity to tuberculin Knies found that old tuberculin was superior to purified protein derivative.

EUGENE H. SMITH, Ogden, Utah.

TUBERCULOSIS TRANSMITTED THROUGH THE PLACENTA. A. GUILBEAULT, A. BERNIER, A. BERTRAND and G. MANSEAU, Union méd. du Canada **68**:610 (June) 1939.

A baby born of a tuberculous mother was immediately removed to another hospital. The baby lost 8 ounces (227 Gm.) during the first four days, but then gained steadily. On the tenth day an ampule of BCG vaccine was given. Two days later fever appeared, and the baby began to lose weight. The baby died on the nineteenth day. Postmortem examination showed extensive generalized tuberculosis. Organisms from the lesions were proved to be of the human rather than of the bovine type. The mother also died and was found to have extensive ulcerative, caseous endometritis. The authors feel that this is a true case of tuberculosis transmitted through the placenta and that BCG activated lesions which were readiy to spread.

VACCINATION AGAINST TUBERCULOSIS WITH BCG. J. BAUDOIN, Union méd. du Canada **69**:396 (April) 1940.

Since 1925, BCG has been administered to nearly 20,000 persons exposed to tuberculosis in Canada, through the cooperation of the University of Montreal, the Pasteur Institute and the National Research Council (Ottawa). The vaccinations were performed on 10,250 infants and children, of whom 9,063 were living in a nontuberculous environment, 793 were in contact with carriers and 394 were in contact with the clinical condition. As controls, a group of 1,606 nonvaccinated children were followed, of whom 1,239 were in contact with carriers and 367 were in contact with clinical patients.

Vaccination with BCG seems to be innocuous. The mortality from tuberculosis has been 69 to 72 per cent lower in the vaccinated group than in the control group. The morbidity rate has been 47 per cent lower in the vaccinated group. The duration of immunity can be studied only by direct means, but it seems to be at least two years.

Baudoin advises that all babies born into families any member of which is known to be tuberculous should be given BCG. DAFFINEE, Boston.

FIRST OBSERVATIONS ON ONE HUNDRED AND SIX CHILDREN VACCINATED WITH PETRAGNANI'S ANATUBERCULIN. F. FERRARO, Med. inf., Rome **10**:157 (June); 189 (July) 1939.

Reports are given of 106 patients, most of them under 1 month of age, who had been exposed to tuberculosis and had received intradermally four injections of Petragnani's "anatuberculin." In each patient a local reaction occurred, and in 59 per cent of the patients an allergy to tuberculin developed and persisted until nine months after the injections. Of the children receiving injections, 21 per cent had died—two thirds from respiratory infections. No untoward results occurred from the vaccinations. The incidence of illness and of death in these vaccinated children did not differ greatly from that seen in previous years, when vaccination was not attempted.

The present report covers the status until nine months after the vaccinations were given. There will be subsequent reports covering a longer period.

HIGGINS, Boston.

FORMS OF CUTANEOUS TUBERCULOSIS IN CHILDHOOD. C. FUNK, Med. Klin. **35**:740 (June 2) 1939.

Funk calls attention to these forms of tuberculosis of the skin so that they may be recognized and the patients treated early. Six photographs are presented. Lupus vulgaris, which is the most common, is discussed in detail. Milk from tuberculous cows is regarded as important etiologically. Cutaneous manifestations accompanying miliary tuberculosis are mentioned.

Erythema nodosum is discussed, particularly as regards causes, the evidence for tuberculosis as the cause not being conclusive. The scrofulous facies is described. Other forms of tuberculosis of the skin, occurring later in life, are also discussed. SIEMSEN, Chicago.

EXAMINATIONS FOR CONGENITAL SYPHILIS IN 3,500 CHILDREN LIVING IN VILLAGES AND FARMS IN HUNGARY. Z. SZENTKIRÁLYI, Orvosi hetil. **83**:126 (Feb. 11) 1939.

These examinations were made in the district of Csongrád. Every child was given a clinical and a serologic examination. It was found that the occurrence of congenital syphilis varies in different regions. The highest rate was 1.9 per cent, but there were many regions where not a single syphilitic child was found. According to the examinations of Neuber, the percentage of syphilitic children living in the larger cities of Hungary is 2. GÖTTSHE, Budapest, Hungary.

EARLY AND LATE PROGNOSIS FOR TUBERCULOSIS IN INFANTS AND YOUNG CHILDREN, WITH A STUDY OF EPITUBERCULOSIS (ELIASBERG-NEULAND). B. SÖDERLING, Acta pædiat. (supp. 2) **23**:1, 1939.

This valuable monograph is 271 pages in length and includes 5 pages of bibliography relating to the prognosis for tuberculosis in children and 4 pages of references to epituberculosis. In addition, more than 60 pages are devoted to reproduction of illustrative roentgenograms, which are, in most cases, first class.

With reference to the prognosis for tuberculosis in infants and children, a review of the literature and a survey of the experience of the children's hospitals in Stockholm during the twenty years between 1914 and 1933 lead to the following authoritative conclusions: Tuberculosis occurring within the first two years of life is an ominous misfortune; infantile tuberculosis remains a fearsome disease. It is doubtful that the prognosis has really improved during the last few years; the apparent betterment may well be due to the more general recognition of cases in which the infection is intrinsically benign. The resources of all agencies, public and private, should be coordinated to prevent tuberculous infection in infancy. Conservative medical therapy has proved disappointing; prophylactic measures should be encouraged. Some encouragement may be drawn from the observation that children who survived an infection acquired during the first two years of life appeared to enjoy immunity to the disease for from five to twenty-five years. About 60 per cent of the surviving children had only a mild primary lesion.

Söderling alines himself with those who regard epituberculosis as a well defined clinical entity, although he admits freely that the diagnosis is often made erroneously. He defines epituberculosis as "a chronic massive lobar, or more than lobar, roentgenographic consolidation of the lung occurring in tuberculous children during the first few years of life." The general condition of the child is little, if any, impaired, and the prognosis is excellent. Inasmuch as the character of the prognosis is an integral part of the concept, the diagnosis cannot be made with assurance in a given case until observation has demonstrated that a favorable outcome is probable. As to the nature of epituberculosis, the author's critical evaluation of the literature and his own clinical experience lead him to the conclusion that it is essentially a lobar collapse of the lung. Its invariably good prognosis suggests strongly that it is a desirable, not an undesirable, complication. This thought leads to the final conclusion that collapse therapy deserves more extensive trial in the treatment of tuberculous infection in infants and young children.

McCUNE, New York.

ABDOMINAL TUBERCULOSIS IN CHILDREN. R. J. HARRENSTEIN, Maandschr. v. kindergeneesk. **9**:442 (Aug.) 1940.

The author presents a discussion of the difficulties encountered in diagnosing abdominal tuberculosis. In many cases these difficulties are increased by the slight sensitivity of the skin to tuberculin. The results of a control examination of 48 children in whose cases the diagnosis had been established by operation are given. It appeared that 42 patients went home cured, remained in good condition and were capable of doing their work.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels, and Spleen

A NEW AND ECONOMICAL DESICCATING PROCESS PARTICULARLY SUITABLE FOR THE PREPARATION OF CONCENTRATED PLASMA OR SERUM FOR INTRAVENOUS USE: THE ADTEVAC PROCESS. JOSEPH M. HILL and DAVID C. PFEIFFER, Ann. Int. Med. **14**:201 (Aug.) 1940.

The apparatus and technic are carefully described. Lyophile serum prepared by this method was used in 45 cases, without unfavorable reactions. The authors consider the use of serum desiccated by this process superior to methods previously in use.

READING, Galveston, Texas.

THE PATHOGENESIS OF BANTI'S DISEASE. WILLIAM P. THOMPSON, Ann. Int. Med. **14**:255 (Aug.) 1940.

A study of 137 cases of Banti's syndrome has convinced the author that portal hypertension associated with normal peripheral venous pressure results in splenomegaly.

In 68 per cent of the cases hepatic cirrhosis was the obstructive factor. Certain extrahepatic lesions were accountable for the splenomegaly in the remainder of the cases. The course of the disease as described by Banti, namely, splenomegaly, hemorrhage and terminal hepatic cirrhosis, was not observed in a single instance in this study.

The author suggests that the term congestive splenomegaly be substituted for the syndrome described as Banti's disease and splenic anemia.

READING, Galveston, Texas.

CERTAIN EFFECTS OF HEMOPHILIA ON THE GROWING SKELETON: SOME ROENTGENOGRAPHIC OBSERVATIONS ON OVERGROWTH AND DYSGENESIS OF THE EPIPHYSES ASSOCIATED WITH CHRONIC HEMARTHROSIS. JOHN CAFFEY and EDWARD R. SCHLESINGER, J. Pediat. **16**:549 (May) 1940.

There have been only a few roentgen studies of hemophilic joints in preadolescence, when the epiphyses are growing and differentiating rapidly. Thomas found that in 89 per cent of 98 hemophiliac patients with hemarthrosis clinical evidence of articular involvement was present before the age of 10 years. The present report is a study of 5 cases chosen from a group of 11 cases of juvenile hemophilia with associated involvement of the joints. In all 5 the development of the epiphyses was advanced; dysgenesis was present in the capitulum of the radius in 2 cases and in the proximal epiphysis of the femur in 1 case. Included in this report is a summary of the clinical, anatomic and roentgen data in the three stages of hemophilic hemarthrosis—acute simple hemarthrosis, panarthritis and the stage of regression.

RAUH, Cincinnati.

APPLICATION IN MAN OF METHOD FOR CONTINUOUS RECIPROCAL TRANSFUSION OF BLOOD. G. G. DUNCAN, L. TOCANTINS and T. D. CUTTLE, Proc. Soc. Exper. Biol. & Med. **44**:196 (May) 1940.

Two human subjects with chronic uremia were given continuous reciprocal blood transfusions with normal adult subjects. Heparin was used as the anticoagulant. The median basilic veins were connected by suitable rubber tubing, which was passed through a roller pump, the same quantity of blood being milked in opposite directions. In the first patient (with polycystic disease of the kidneys) there was an exchange of 2.520 cc. of blood (including heparin and saline solution) in two hours and fifty minutes and in the second (with chronic glomerulonephritis) 7,020 cc. of blood in forty-seven minutes. In neither study were there any untoward effects, and clinically both patients seemed improved. An increase in excretion of nitrogen in the urine occurred in the donor subjects.

HANSEN, Minneapolis.

SERUM PHOSPHATASE, CALCIUM AND PHOSPHORUS VALUES IN INFANCY. D. J. BARNES and B. MUNKS, Proc. Soc. Exper. Biol. & Med. **44**:327 (June) 1940.

In this study 630 observations were made (on 390 normal babies from a large hospital and follow-up clinic and on 240 babies referred from the child welfare stations because they were thought to be rachitic and in need of treatment) as regards the serum calcium, phosphorus and phosphatase values. The values for serum calcium and serum phosphorus in the two groups of babies were similar. During the early months the values for serum phosphatase were slightly higher for the babies from the welfare clinic than for the control group. This was taken to indicate that an increase in serum phosphatase is the earliest reliable sign of rickets. During the rest of the first year the values in the two groups were similar, no essential change occurring with the season.

HANSEN, Minneapolis.

THE SCHULTZ SYNDROME (GRANULOCYTOPENIA), WITH SPECIAL REFERENCE TO ITS TREATMENT WITH EXTRACT OF YELLOW BONE MARROW. E. B. DREVERMANN and H. J. GARDNER, M. J. Australia **1**:851 (June 22) 1940.

The literature on granulocytopenia is reviewed. The preparation of extract of yellow bone is described. On the basis of a limited experience in the treatment of granulocytopenia the authors feel that they cannot suggest that marrow extract is specific in all cases. They state that it should be used in conjunction with pentnucleotide.

GONCE, Madison, Wis.

A CASE OF ACUTE EOSINOPHILIC LEUKAEMIA. D. REYE, M. J. Australia **2**:156 (Aug. 17) 1940.

A case is described in which a high eosinophil count was associated with death from heart failure due to multiple infarctions. Too many of the characteristic features of leukemia were lacking to warrant the diagnosis of acute eosinophilic leukemia.

GONCE, Madison, Wis.

ANAEMIA WITH SPLENOMEGALY. DONALD PATERSON, Proc. Roy. Soc. Med. **33**: 372 (May) 1940.

The case of a girl of 6 years is reported. From birth the abdomen had appeared abnormally large. At the age of 2 years she had a severe attack of jaundice, which after an acute phase of two weeks had persisted in a slight degree. She had had three severe hematemeses in twelve hours, after which she gradually had put on weight and appeared quite well for nine months, after which time she had three further hematemeses. After admission to the hospital she improved for a month; then she had three more attacks of bleeding. The family history, physical examination and investigations are included in the report.

WILLIAMSON, New Orleans.

LEUKOCYTES OF CHILDREN UNDER TREATMENT WITH SULFANILAMIDE. B. VASILE, Med. inf., Rome **11**:95 (April) 1940.

Studies of the blood of 24 children under treatment with sulfanilamide from five to twenty-four days revealed no modification in the number or character of the white cells which could be ascribed to the drug.

HIGGINS, Boston.

ACETONE BODIES IN THE BLOOD OF INFANTS. E. SCHWARZ, Med. ital. **20**:477 (Oct.) 1939.

The author discusses the etiology, laboratory picture and diagnosis of acidosis. He reviews the mechanism of formation of acetone bodies.

MARTOCCIO, Utica, N. Y.

CHRONIC ERYTHROBLASTIC ANEMIA (SYNDROME OF COOLEY). C. GRILLO, Pediatria **47**:791 (Sept.) 1939.

The author presents a very complete work-up of the case of an 8 year old child three years after the child was seen for the first time. No measurements seem to have been omitted in this case. Anthropometric measurements, photographs and roentgenograms of the skull, long bones, hands and feet are shown. There was marked hypochromic anemia, with erythroblasts and leukocytosis in the peripheral circulation. Examination of the bone marrow showed a marked increase of cells of the red series over those of the white. There was increased resistance of the red cells. There was marked osteoporosis. The cause was not known. The author feels that malaria may have been a cause.

MARTOCCIO, Utica, N. Y.

DIAGNOSTIC DIFFICULTIES OF LEUKEMIA IN CHILDHOOD. C. HOOFT and L. VERHOESTRAETE, Maandschr. v. kindergeneesk. **9**:279 (April) 1940.

The authors give a description of 2 cases of lymphatic leukemia in childhood. The patient in the first was a boy 8 years old, with subacute aleukemic leukemia simulating aplastic anemia with septicemia. The patient in the second was a girl nearly 6 years old who presented some typical osseous changes. The authors note the presence of atypical immature lymphocytes known in the German literature as paralymphoblasts. They emphasize the difficulty which may arise in obtaining a correct diagnosis of the pathologic cell type as well as of the leukemic condition itself. They summarize the various known osseous changes.

VAN CREVELD, Amsterdam, Netherlands.

ARTICULAR SYMPTOMS IN LEUKEMIA. T. HALBERTSMA, Maandschr. v. kindergeneesk. **9**:307 (May) 1940.

The author describes a case of subchronic, subleukemic lymphatic leukemia characterized by intermittent pains and swellings of the joints in a girl 10 years old. Differentiation from acute rheumatism, sepsis and Still's disease gave great difficulties, notwithstanding a thorough examination. At autopsy the diagnosis of leukemia was fully confirmed. A discussion of analogous cases in the literature is added.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Nose, Throat and Ear

POSTURAL TREATMENT OF ACUTE LARYNGOTRACHEOBRONCHITIS. T. C. GALLOWAY, J. A. M. A. **112**:1566 (April 22) 1939.

Galloway describes the clinical picture of this condition and the mechanism of production of sudden asphyxiation. Advocating tracheotomy, bronchoscopy and respiratory lavage, the author concludes from his experience with the 10 cases reported that postural drainage as an adjunct in treatment needs emphasis and is of great value.

HEERSMA, Kalamazoo, Mich.

THE VALUE OF SULFANILAMIDE IN OTOGENOUS INFECTIONS. JACOB L. MAYBAUM, EUGENE R. SNYDER and LESTER L. COLEMAN, J. A. M. A. **112**:2589 (June 24) 1939.

The authors present case records to illustrate instances in which the use of sulfanilamide altered the clinical picture from what would usually be expected. Not to detract from the drug's usefulness, they urge its use for nonsuppurative otitis media and for complications of aural disease produced by certain bacteria when adequate drainage of the focus has been established.

However, in the period of observation of aural disease when mastoiditis, sinus thrombosis, petrositis and the like are suspected, sulfanilamide should not be given, as it will obscure the picture and the course of meningitis or abscess of the brain may be distinctly altered by its use.

HEERSMA, Kalamazoo, Mich.

THE SIGNIFICANCE OF ACCESSORY SINUS DISEASE IN CHILDREN. ALFRED WACHSBERGER, M. Clin. North America **23**:681 (May) 1939.

Sinal infections in infancy and childhood hold a greater potential danger than in adult life. Infection occurring during the period of pneumatization of these structures may permanently arrest this process. Lack of normal pneumatization may lead to lifelong chronic infection.

Infection originating in the sinuses may attack structures (such as surrounding periosteum and bone) by direct local extension or by transmission by way of the lymph channels to the lower levels of the respiratory system. A common mode of extension is by continuity of tissue to the bronchi and lungs. Chronic

bronchitis, frequently bronchiectasis and occasionally pulmonary abscess may be traced to nasal infections.

The mechanical importance of free nasal airways must be emphasized. Ventilation of the sinuses depends on alternate changes in air pressure, negative with inspiration and positive with expiration. Any interference with this mechanism may result in obstruction to the ostiums, retention of secretions within the sinuses and possible suppuration.

EUGENE H. SMITH, Ogden, Utah.

THE MANAGEMENT OF ORGANIC FOREIGN BODIES IN THE TRACHEA AND BRONCHI OF CHILDREN—ILLUSTRATED WITH LANTERN SLIDES. ELBYRNE G. GILL, Virginia M. Monthly **66**:275 (May) 1939.

Thirty-six cases are reported in which vegetable foreign bodies were aspirated into the trachea and bronchi of children aged 7 months to 11 years. The foreign bodies in the order of frequency were peanuts, walnuts, corn, beans, chestnuts, apple, coconut and watermelon seed. All were removed bronchoscopically except two which were removed through a tracheotomy wound and four which were removed by coughing. Emphasis is placed on the importance of obtaining a careful history in cases of unexplained cough and irregular but persistent fever in children. Roentgen examination and careful physical examination should be made, and in the presence of signs and symptoms suggestive of a foreign body, bronchoscopic procedures should be used. The three signs most often found are: (1) unilateral limitation of expansion of the lung and chest on the affected side; (2) hyperresonance on percussion, and (3) diminution or total absence of the breath sounds.

For anesthesia during bronchoscopic procedures the author uses sodium amytal administered by bowel, together with ether given with extreme caution by the drop method.

As to complications, tracheobronchitis present prior to operation continued in 6 cases and bronchopneumonia occurred in 2 cases. Tracheotomy was done in 9 cases—to relieve postoperative edema, dyspnea prior to or immediately following bronchoscopic procedures and in 1 case for drainage of a pulmonary abscess. In the 36 cases there were 35 recoveries. The 1 death was due to general sepsis secondary to pulmonary abscess in a child admitted to the hospital in a moribund condition.

STONE, Richmond, Va.

LATENT OTITIS AND DISTURBANCES OF NUTRITION IN INFANTS. U. FERRI, Lattante **10**:143 (April) 1939.

There is a difference of opinion among pediatricians as to the importance of latent otitis media, mastoiditis and antral infection as a cause of severe gastroenteritis. In many cases operations on the antrum or on the mastoid have indicated that they were not the predominating factor in the nutritional disturbance. However, in a case of diarrhea which is running an acute or subacute course and is not responding to the usual dietetic and constitutional treatment, one should not hesitate to resort to operation as a possible means of relief.

HIGGINS, Boston.

OTITIS AND OTOMASTOIDITIS IN THE NURSLING. I. TOMA, MARIA GEORGESCU and V. PETRESCU-COMAN, Med. inf., Bucuresti **1**:277 (May-June) 1939.

Otitis is frequently encountered in nurslings in institutions. Thirty-seven and seven-tenths per cent of the nurslings hospitalized at the Institute for Puericulture have had otogenic infections. Otitis in the nursling can present different clinical aspects: acute otitis, subacute otitis, latent otitis and finally otomastoiditis. Forms of a great deal of importance from a diagnostic standpoint are subacute otitis, latent otitis and mastoiditis. Behind a picture characterized clinically by fever, grave gastrointestinal troubles, extensive loss of weight and the different signs of

otitis disguised or absent, there often occurs hidden or subacute otitis. In the course of latent otitis, signs of involvement of the ear may be absent; digestive troubles as well as temperature are variable in intensity and nature. The state of nutrition dominates the clinical picture. In otomastoiditis, the general condition of the patient, digestive disturbances (uncontrollable vomiting and diarrhea), high fever, catastrophic loss of weight and hyperleukocytosis are the chief elements in diagnosis. The clinical picture under which latent otitis presents itself may cause the condition to be recognized only at autopsy. In cases of such a clinical picture as has been described, it is preferable to practice repeated puncture, or paracentesis, of the drum than to allow otitis to develop with its serious consequences. In the course of otomastoiditis energetic medical treatment rarely gives satisfactory results. In no case ought one to temporize, awaiting results from this treatment. The pediatrician is more competent than the otologist to fix the time of intervention. This should be practiced with the region under local anesthesia and should be done rapidly.

FROM THE AUTHORS' SUMMARY.

Diseases of Lungs, Pleura and Mediastinum

POST-TONSILLECTOMY PULMONARY ABSCESS (PREABSCESS STAGE) ABORTED WITH SULFAPYRIDINE. KARL MUSSER HOUSER and THOMAS FITZ-HUGH JR., Arch. Otolaryng. **31**:855 (May) 1940.

The authors outline the case of a 42 year old woman with a severe pulmonary suppuration, apparently due to post-tonsillectomy embolism and treated successfully with sulfapyridine. The drug is stated to be of definite value in such cases if employed in the "pneumonic stage." Attention is called to the fact that a potentially serious "sensitization reaction" to sulfanilamide is no contraindication to the successful use of sulfapyridine.

GREENWOOD, Chicago.

PRESENT TRENDS IN THE TREATMENT OF PNEUMONIA IN CHILDREN. WILLIAM C. EMM, New York State J. Med. **40**:241 (Feb. 15) 1940.

The cases of 515 children with pneumonia admitted to the Syracuse Memorial Hospital from 1934 to 1939 are reported. The cases were divided almost evenly between lobar pneumonia and bronchopneumonia. In patients under 2 years of age bronchopneumonia predominated. The mortality of the series was 15.4 per cent. Specific serum was used in 40 cases. Sulfapyridine was highly effective in the few cases in which it was used.

AIKMAN, Rochester, N. Y.

THE USE OF SULFANILAMIDE IN THE TREATMENT OF HEMOLYTIC STREPTOCOCCIC EMPYEMA. LEON J. LEAHY, New York State J. Med. **40**:347 (March 1) 1940.

Six cases of streptococcic empyema in children are reported, and in 3 of the proved cases no drainage was required. In but 1 case was there no apparent effect from the drug. While results are not uniform, the use of sulfanilamide for streptococcic empyema reduces the necessity of drainage and improves the general results.

AIKMAN, Rochester, N. Y.

BRONCHOPLEURAL FISTULA (A REPORT OF A CASE COMPLICATING AN ENCYSTED PYOTHORAX WITH UNUSUAL ROENTGEN FINDINGS). BERNARD L. PACELLA and GEORGE E. BROCKWAY, New York State J. Med. **40**:374 (March 1) 1940.

The case is reported of an 11 year old boy in whom the condition followed pneumonia. Frequent expectoration of mucopurulent sputum led to the diagnosis of bronchopleural fistula. Methylene blue was injected in the right pleural cavity, and four minutes later blue-stained sputum was obtained. No operative drainage was attempted, and the child made a good recovery.

AIKMAN, Rochester, N. Y.

EFFICACY OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA IN INFANTS. L.-C. SIMARD and A. GUILBEAULT, Union méd. du Canada **69**:244 (March) 1940.

At Notre Dame Hospital in Montreal, Canada, the mortality rate of pneumonia in infants has been reduced since sulfapyridine has been used. From September 1936 to September 1937 the mortality was 32.5 per cent; in 1937-1938 it was 29 per cent. In 1938-1939, with the use of sulfapyridine, it dropped to 7.6 per cent.

Sulfapyridine is given during the day of admission in six doses, with a total of 1½ grains (0.9 Gm.) per pound of body weight. The following day the dose is 1 grain (0.06 Gm.) per pound, and this amount is given until the temperature has been normal for two or three days.

DAFFINEE, Boston.

OTITIS MEDIA AS A PRECURSORY SYMPTOM OF PNEUMONIA IN CHILDHOOD. H. W. GÖRGES, Med. Klin. **36**:190 (Feb. 16) 1940.

The author points out that pneumonia not infrequently develops during an attack of otitis media or four to seven days after its subsidence. He stresses adequate care of otitis media as a prophylactic measure against pneumonia.

SIEMSEN, Chicago.

APPLICATION OF THE ROENTGEN CAMERA PHOTOGRAPHY (SCREEN PHOTOGRAPHY) IN THE ROENTGEN EXAMINATION OF THE LUNGS IN CHILDHOOD. G. C. E. BURGER, Maandschr. v. kindergeneesk. **9**:187 (Feb.) 1940.

The author sets forth the progress in the roentgen examination of the lungs obtained by using roentgen camera photography. This recent method allows a serial examination which can be performed by a nonspecialized personnel. With this method the price of the roentgenograms is greatly reduced; consequently the field of examination can be greatly extended, with the result that many unsuspected changes may be detected.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CONGENITAL ANOMALIES OF THE DUODENUM. JOHN B. DE C. M. SAUNDERS and HAROLD H. LINDNER, Ann. Surg. **112**:321 (Sept.) 1940.

Because of the rarity of this condition, the authors report in detail 3 cases which have come under their observation.

Pathologically, congenital duodenal obstruction has been found to result from the effects of either intrinsic or extrinsic factors. Extrinsic obstruction is the result of either developmental error or prenatal pathologic processes. Intrinsic obstruction is the outcome of atresia, stenosis or valve formation.

Duodenal obstruction will give the signs common to high intestinal obstruction. Hematemesis and the presence of coffee-ground vomitus in the absence of a blood dyscrasia are pathognomonic of duodenal atresia. Absolute constipation is the rule. The roentgenogram is of value in making the diagnosis, and it should be remembered that children with true hypertrophic pyloric stenosis do not vomit until the seventh or ninth day at the earliest, whereas infants with duodenal obstructions vomit as early as the first twenty-four hours.

The treatment is essentially surgical and should be undertaken as soon as the physical condition of the patient warrants it.

BANTIN, Omaha.

STUDIES IN THE ETIOLOGY OF ACUTE APPENDICITIS. CLARENCE DENNIS, RAYMOND E. BUIRGE, RICHARD L. VARCO and OWEN H. WANGENSTEEN, Arch. Surg. **40**:929 (May) 1940.

Experiments were carried on in rabbits to determine the secretory capacity of the rabbit cecal appendage and the effects of increased intraluminal tension. It was

shown definitely that the cecal appendage of the rabbit secretes fluid in large amounts and is capable of secreting against a pressure of about 100 cm. of water. When the base is obstructed, the intraluminal pressure is elevated by this outpouring of fluid and acute appendicitis develops in four to six hours with rupture in eight, the process going on to peritonitis, abscess formation, widespread adhesions and ultimately death of the animal. This process simulates all the pathologic manifestations of the human disease.

KAISER, Rochester, N. Y.

EFFECT OF ATROPINE ON THE GASTRO-INTESTINAL TRACT FOLLOWING THYROID MEDICATION. SAMUEL MORRISON and MAURICE FELDMAN, Endocrinology **27**:500 (Sept.) 1940.

Experiments on dogs demonstrated that atropine inhibits gastric motility in the normal animal. Bilateral vagotomy decreases the gastric motility.

The administration of desiccated thyroid gland overcomes the inhibited gastric motility resulting from bilateral vagotomy but not that resulting from atropine.

JACOBSEN, Buffalo.

CREAM-FILLED PASTRIES RESPONSIBLE FOR GASTROENTERITIS. Health News **17**:123 (July 22) 1940.

Fifteen cases of gastroenteritis among members of four households in Nassau County were found to be due to custard pastries procured from one bakery. A direct smear of the custard filling of chocolate eclairs, strawberry tarts and custard-filled cakes revealed staphylococci.

AIKMAN, Rochester, N. Y.

GASTROENTERITIS IN ROSCOE BELIEVED DUE TO RAW MILK. Health News **17**:141 (Aug. 19) 1940.

Eighty-three cases of milk-borne infection occurred among the patrons of a raw milk dairy.

AIKMAN, Rochester, N. Y.

GASTROENTERITIS BELIEVED DUE TO ICE CREAM. Health News **17**:143 (Aug. 26) 1940.

Two hundred children and 31 adults, all occupants of a camp, became ill with gastroenteritis. It is believed that the infection was due to ice cream furnished to the camp in paper containers.

AIKMAN, Rochester, N. Y.

THE INFLUENCE OF THE FOODSTUFFS UPON THE SUSCEPTIBILITY OF THE LIVER TO INJURY BY CHLOROFORM, AND THE PROBABLE MECHANISM OF THEIR ACTION. SAMUEL GOLDSCHMIDT, HARRY M. VARS and ISIDOR S. RAVDIN, J. Clin. Investigation **18**:277 (May) 1939.

By administration of different diets, groups of rats were obtained for which the level of hepatic lipid varied from 8.6 to 62.4 per cent of fatty acids by dry weight and for which the level of hepatic glycogen was high or low at any given level of lipid concentration. These rats were anesthetized with chloroform under standardized conditions, and twenty-four hours later their livers were analyzed for glycogen and fatty acid content and examined histologically.

The incidence and severity of damage to hepatic cells increased progressively with increased concentration of lipids in the liver and independently of the glycogen content of the liver at the beginning of the chloroform anesthesia. A high concentration of glycogen per se failed to confer protection against the hepatotoxic action of chloroform in rats with the same concentration of hepatic fatty acids and a similar intake of protein in the diet.

A high protein diet administered prior to the chloroform anesthesia reduced the incidence of hepatic cellular necrosis even in livers with a high lipid content.

GUEST, Cincinnati.

THE NORMAL FECAL FLORA OF INFANTS BETWEEN TWO WEEKS AND ONE YEAR OF AGE. M. L. SNYDER, J. Infect. Dis. **66**:1 (Jan.-Feb.) 1940.

"Examination of the feces of a group of 22 infants under one year of age showed that while many species of bacteria were isolated only a few were present enough times to be considered as possible members of the normal fecal flora, even with 25% selected for the lowest figure. This dominance of the fecal picture by a few species might well be assumed on the basis of our knowledge of the fecal flora, the factors influencing growth in the intestinal tract, and the culture mediums employed. This work confirmed the assertion of Davidson who stated that only a half-dozen species made up the normal fecal flora of man, but he did not give the species or the order of their occurrence. In the present study the following species occurred in more than 25% of the stools examined: (1) Bact. coli, 93.4%; (2) Str. fecalis, 78.5%; (3) B. welchii, 68.7%; (4) B. tertius, 51.6%; (5) Bacteroides, group I, 47%; (6) Bact. aerogenes, 44%; (7) Str. mitis, 29.7%; (8) M. epidermidis, 26.4%; (9) L. bifidus, 24.2%. L. bifidus must be considered to be uniformly present in stools of nurslings and predominant in supplemented breast-fed babies. The total percentage for L. bifidus was therefore greatly influenced by the preponderance of stools from weaned babies.

"Although the changes, microscopically and culturally in respect to L. bifidus, of infant stools as associated with the feeding of mother's milk have long been known, the influence of apparently normal diets on the remainder of the fecal flora is quite obscure. It would not seem illogical, and it was shown, that the expectancy of finding any bacterial species in the feces, except possibly the streptococci, would depend not so much on the child as on the diet. Thus, Bact. aerogenes and Bact. coli-mutabile were less frequently isolated from the stools of breast-fed babies than from those of weaned babies. There is no question but that the breast milk stool is inhibitory to the growth of sporulating anaerobes; only four strains of B. welchii were recovered from the stools of the breast-fed group. However, as soon as the infants received supplement in addition to the breast feedings, then various species appeared in their stools with saccharolytic forms far more common than proteolytic varieties. The tiny gram-negative non-sporulating anaerobes were also isolated, with far more regularity after weaning than before. On the other hand, the staphylococci seemed to be encountered more frequently in the early period of breast and supplemented breast feeding periods than in later months.

"These data are admittedly incomplete, especially with the genus Lactobacillus and genus Bacteroides, but it is hoped that they point the way toward a more accurate knowledge of the bacteria in the feces of infants under one year of age, and a better understanding of the physiological roles which these species may play in health and disease."

AUTHOR'S SUMMARY.

ON THE PROBLEM OF DIARRHEAS OF CHILDHOOD: A STUDY OF 543 ATTACKS IN CHILDREN IN BEIRUT, SYRIA. J. LEONARD MOORE and E. WESTERVELT DENNIS, J. Lab. & Clin. Med. **25**:955 (June) 1940.

The conditions studied were of the so-called nonspecific type. Four hundred and ninety patients were observed. The conclusion reached was that diarrhea is a clinical entity of which "dysentery" and "simple diarrhea" are phases. In the absence of competent laboratory examination any assumption as to the noninfectiousness of diarrhea in any case is unjustified and dangerous.

READING, Galveston, Texas.

CONGENITAL FAMILIAL STEATORRHEA WITH FIBROMATOSIS OF THE PANCREAS AND BRONCHIOLECTASIS. SOLOMON RAUCH, ABRAHAM M. LITVAK and MATTHEW STEINER, J. Pediat. **14**:462 (April) 1939.

Two cases of congenital familial steatorrhea with fibromatosis of the pancreas and bronchiolectasis are presented, 1 with postmortem observations. The past and present concepts of the terms "steatorrhea" and "celiac syndrome" are

reviewed, and the clinicopathologic complex of steatorrhea with fibromatosis of the pancreas and bronchiolectasis is differentiated from the classic syndrome of celiac disease. The steatorrheas are classified as the idiopathic variety, including celiac disease, and the pancreatogenous variety. In the latter division fall most of the cases reported in the literature, in which the condition begins soon after birth and is refractory to treatment. Postmortem examinations show fibromatosis in the pancreas. The association of respiratory symptoms and pulmonary findings with the steatorrheas is discussed, and the reasons for considering the pathologic phenomena of both pancreas and bronchi to be based on congenital anomalies are given.

RAUH, Cincinnati.

THE RELATION OF DYSENTERY TO THE ACUTE DIARRHEA OF INFANTS AND CHILDREN. MERLIN L. COOPER and others, J. Pediat. **15**:172 (Aug.) 1939.

"An intensive study on the stools of infants and children suffering from acute diarrhea was carried out on 209 patients during the summer of 1938.

"From 102 patients (49 per cent) dysentery organisms were recovered.

"The seasonal incidence, case fatality rate and duration of gastro-enteritis were not significantly different in the dysentery and nondysentery groups.

"The frequency distribution of the two groups according to the age of the patient was strikingly different. Seventy-five per cent of the patients under 1 year of age did not have dysentery while 75 per cent of those over 1 year did.

"The data have been analyzed statistically from the standpoint of the efficiency of several culture media used. Sodium desoxycholate citrate medium is markedly superior for isolating dysentery organisms."

AUTHORS' SUMMARY.

VITAMIN A ABSORPTION IN CATARRHAL JAUNDICE. B. B. BREESE and AUGUSTA B. MCCOORD, J. Pediat. **16**:139 (Feb.) 1940.

A series of tests for the absorption of vitamin A was performed on 21 patients with catarrhal jaundice, who had been observed for eight years. The tests were done in the following manner. After a basal sample of blood was taken, a measured amount of fish liver oil of high potency was given by mouth, and samples of blood were taken at intervals of two, four, six, nine, twelve and twenty-four hours. These samples were analyzed for vitamin A by the method of Carr and Price as modified by McCoord and Clausen. The maximum amount of vitamin A in the blood of a patient whose absorption is normal is found four hours after ingestion of the oil and averages 170 blue units (1 blue unit is approximately equivalent to between 3.5 and 4 U. S. P. units) of vitamin A per hundred cubic centimeters of blood. The results of these tests showed that in cases of catarrhal jaundice in the active stage, vitamin A is usually poorly absorbed when given by mouth. With improvement in the condition the rise in vitamin A in the blood of the patient after ingestion is equal to or higher than that of the normal person. The administration of bile salts by mouth in adequate amounts seemed to aid in the absorption of vitamin A.

RAUH, Cincinnati.

THE PATHOLOGY AND BACTERIOLOGY OF ILEOCOLITIS IN CHILDREN. B. BARRERA, J. Philippine Islands M. A. **19**:345 (June) 1939.

This report embraces a postmortem study of 265 children under 5 years of age. Of these, 177 died with symptoms of ileocolitis. Scrapings from the mucosa of the colon and of the terminal portion of the ileum were inoculated into plain broth and after incubation were followed bacteriologically on suitable mediums.

The condition in the majority of the 177 cases studied was catarrhal, results of bacteriologic studies being variable and suggestive of food intoxication rather than of true infection. Children under 1 year of age apparently suffer more from this type of ileocolitis, whereas older children are more likely to have typical

bacillary dysentery, the Flexner type being most frequently encountered. Sugar reactions furnish one of the most valuable guides in the identification of micro-organisms, according to Barrera, and they should be observed for at least two weeks in order to avoid possible errors. The bacteriologic findings are presented in tabular form.

WEIGAND, Indianapolis.

ACUTE PANCREATITIS. JOHN J. MORTON, New York State J. Med. **40**:255 (Feb. 15) 1940.

This thorough study is based on a series of cases from the Strong Memorial Hospital in Rochester.

AIKMAN, Rochester, N. Y.

CARCINOMA OF THE COLON OCCURRING IN A GIRL OF 13 YEARS. WILLIAM B. RAWLS, New York State J. Med. **40**:290 (Feb. 15) 1940.

A fatal case of this rare condition in a 13 year old girl is reported.

AIKMAN, Rochester, N. Y.

PRODUCTION OF CIRRHOSIS OF THE LIVER OF THE NORMAL DOG BY HIGH FAT DIETS. I. L. CHAIKOFF and C. L. CONNOR, Proc. Soc. Exper. Biol. & Med. **43**:638 (April) 1940.

Four dogs fed on a high fat diet died one hundred and thirty-eight, two hundred and forty-six, two hundred and ninety-eight and three hundred and eighty-six days after institution of this regimen. In all 4 animals severe fatty infiltration was found in the liver, and in 3 severe diffuse fibrosis (cirrhosis) was present.

HANSEN, Minneapolis.

THE LEVULOSE TOLERANCE TEST IN CHILDHOOD. J. C. THOMPSON and A. W. WILKINSON, Edinburgh M. J. **47**:250 (April) 1940.

The author speaks of the renewal of interest in the levulose tolerance test of hepatic function. The liver is chiefly concerned in the metabolism of levulose. Recently the estimation of this substance in the presence of an increased amount of dextrose has been made simple and reliable by micromethods. The author gives the technic and results, first using normal subjects and later doing twenty tests on children who had been given an anesthetic a few days before the test. Children with various diseases and operative procedures were tested; among these were patients with burns and scalds, icterus neonatorum and renal diseases and children who had been given large amounts of sulfanilamide.

Abnormal results were obtained after anesthesia in children who made a rapid recovery. This would indicate a transient impairment of the liver. Damage to the liver was evidenced in the children who had suffered from burns and who had had varying amounts of chemotherapy. A normal curve was found in a fatal case of icterus neonatorum, verified by evidence at autopsy of freedom from gross damage to the liver. There were abnormal findings in 2 instances of renal disease.

NEFF, Kansas City, Mo.

PYLORIC STENOSIS AND PSEUDOSTENOSIS. E. TERRIEN, Presse méd. **48**:86 (Jan. 24-27) 1940.

Terrien points out the difficulties of differentiating between a true stenosis and pseudostenosis (pylorospasm). In the presence of the pyloric syndrome (projectile vomiting, constipation and rapid loss of weight), medical treatment should first be tried. Placing the infant on his stomach after eating, administering small thickened feedings or lavage of the stomach followed by immediate gavage may produce a cure of pylorospasm.

DAFFINEE, Boston.

MECHANICAL PHENOMENA OF THE STOMACH OF THE INFANT DURING DIGESTION. G. FROLLO, Pediatria **47**:782 (Sept.) 1939.

The author took roentgenograms of 20 infants under 6 months of age. Pictures of the stomach were taken every few minutes from the start of nursing to the end. All the infants were breast fed. After the first sucking movements there was a rapid increase in the size of the stomach, and it reached its greatest fulness after about ten minutes in all the infants. The stomach retained its shape until the end of the feeding, which lasted about twenty to twenty-five minutes. The author feels that this rapid distention cannot be explained only by swallowed air but is due to a reflex stimulation of the muscle fibers due to the milk entering the stomach or to the sucking movements.

MARTOCCIO, Utica, N. Y.

HUMAN MYCOSES; THE INTESTINAL MYCOTORULAE OF CHILDREN. V. SAGGESE, Riv. di clin. pediat. **38**:1 (Jan.) 1940.

The stools of 7 children with diarrhea were found to contain pathogenic mycotorulae consistently and in large amounts. Stools of 6 contained Mycotorula albicans; of 2, Mycocandida pseudotropicalis; of 1, Pichia chodati, and of 1, Rhodotorula mucilaginosa. Cultures of these fungi proved pathogenic to rabbits. The growths in the cultures were more quickly killed by solutions of potassium arsenite than by potassium iodide. The therapeutic response also was better to arsenic than to iodide.

HIGGINS, Boston.

THREE CASES OF HYPERTROPHIC STENOSIS OF THE PYLORUS. A. GENTILI, Riv. di clin. pediat. **38**:366 (June) 1940.

Three infants with pyloric stenosis, a girl and 2 boys, were operated on successfully by the Ramsted-Fredet technic.

HIGGINS, Boston.

HYDRATION OF PATIENTS WITH TOXICOSIS IN RELATION TO THE HUMORAL TABLE. PEDRO COFRE G. and IVAN PRIETO N., Bol. Inst. internac. am. de protec. a la infancia **13**:716 (April) 1940.

The authors refer to the importance of the problem of hydration in the fight against toxicosis in the infant. They believe that the fluids used for parenteral injections should be related to the changes produced by the toxicosis in the organism. The authors studied the alkaline reserve, the globular chlorine, the plasma chlorine and the blood urea, and only after these studies did they administer the necessary fluid.

FROM EDITOR'S SUMMARY.

Nervous Diseases

THE BIOCHEMISTRY OF EPILEPSY. H. GOLDSTEIN and R. A. MCFARLAND, Am. J. Psychiat. **96**:771, 1940.

Goldstein and McFarland in a comprehensive review of the literature found few clearcut and definite biochemical abnormalities associated with epilepsy. They gained the impression, rather, that the abnormality consists of a greater variability in the constituents. As a result of the seizure there are an increase in sugar and in calcium in the blood and, depending on the severity of the attack, a decrease in the p_H. These findings, however, are not statistically reliable. There is no conclusive evidence that seizures are related to abnormalities of dextrose tolerance. The hour to hour variation and the daily range of the p_H appear to be greater in epileptic than in normal persons. As a result of the seizure there is slight temporary acidosis. Studies of blood gases have not revealed generalized cerebral anoxemia, nor is induction of this state a certain method of producing seizures. No correlation has been found between calcium values and epileptic seizures, but the blood calcium values for epileptic persons show a wider range than normal.

Studies of protein metabolism have been negative for the most part. An increase of fibrinogen in the blood is the only chemical abnormality found in epileptic subjects. Nitrogen retention seems to be an effect rather than a cause of the seizure. Low cholesterol values with wide variability are reported, but correlation between this and seizures is not definite.

FORSTER, Boston. [ARCH. NEUROL. & PSYCHIAT.]

SPREAD OF THE EPILEPTIC DISCHARGE: AN EXPERIMENTAL STUDY OF THE AFTER-DISCHARGE INDUCED BY ELECTRICAL STIMULATION OF THE CEREBRAL CORTEX. THEODORE C. ERICKSON, Arch. Neurol. & Psychiat. **43**:429 (March) 1940.

The author studied the after-discharge induced by electrical stimulation of the cortex of monkeys with the assumption that they are the same as electrical fits in man. That the corpus callosum plays a definite role in the spread of the epileptic discharge from one hemisphere to the other was demonstrated by surgical transection of the cortex.

The author also concluded that the subcortical centers play a part in the spread of the discharge when the cerebral cortex is intact and that the discharge takes place by neuronal pathways.

BEVERLY, Chicago.

PRIMARY CORTICAL CENTERS FOR MOVEMENTS OF UPPER AND LOWER EXTREMITIES: OBSERVATIONS BASED ON ELECTRICAL STIMULATION. JOHN E. SCARFF, Arch. Neurol. & Psychiat. **44**:243 (Aug.) 1940.

This is a very well written, detailed article. It has been assumed that the primary cortical centers for the lower extremities in man are situated on the lateral convexity of the cerebral hemisphere. Observations made after the results of electrical stimulation in 14 cases indicate that the primary motor area for the upper extremity commonly extends upward on the lateral surface of the cerebral hemisphere as far as its superior mesial border, while the leg, as a rule, is represented only on the mesial surface of the cerebrum.

BEVERLY, Chicago.

RELATION OF INTRACRANIAL TUMORS AND SYMPTOMATIC EPILEPSY. WILDER PENFIELD, T. C. ERICKSON and I. TARLOV, Arch. Neurol. & Psychiat. **44**:300 (Aug.) 1940.

"The slowly growing neoplasms have a higher incidence of secondary epilepsy than the rapidly growing tumors, probably because death terminates the history sooner in cases of the latter type. Seizures form a first symptom also more frequently in cases of the slowly growing tumors. Infiltrating and encapsulated tumors, if they are equally slow growing, have an approximately equal incidence of seizures. Operative removal gives complete relief from seizures twice as often in cases of encapsulated tumors as it does in cases of infiltrating tumors. In our clinic the percentage of 'cure' of seizures by operative removal of encapsulated tumors is about the same as that from excision of focal cerebral scars for the relief of epilepsy.

"Abscesses of the brain are apt to produce seizures at an early stage and again after the formation of a healed scar. Subdural hematomas have a relatively low incidence of seizures, and the attacks even then seem to be due to cerebral injury that may have resulted from trauma rather than to the hematoma itself."

BEVERLY, Chicago.

RELATION OF AGE TO MOTOR IMPAIRMENT IN MAN AND IN SUBHUMAN PRIMATES. MARGARET A. KENNARD, Arch. Neurol. & Psychiat. **44**:377 (Aug.) 1940.

The central nervous system of the infant is potentially different from that of the adult, as manifested by the motor deficits which appear after known cortical

ablations. The absence of cortical motor areas in the infant is not accompanied with signs of motor deficits before complex skilled motor activity is developed. Spasticity begins to appear much later than paresis.

BEVERLY, Chicago.

CATALEPSY IN A MALE INFANT. J. L. ROGATZ and M. PICKER, Arch. Pediat. **56:** 444 (July) 1939.

A 22 month old boy showed catalepsy. He was markedly malnourished and presented clinical evidence of rickets.

ORR, Buffalo.

STAPHYLOCOCCUS AUREUS MENINGITIS. D. C. PEWTERBAUGH, Arch. Pediat. **56:** 623 (Oct.) 1939.

A 4 year old boy recovered from meningitis and septicemia, both due to infection with Staphylococcus aureus. The meningitis was of the primary type. Organisms were found in direct smears of the spinal fluid. Specimens were taken daily until the tenth day. Blood cultures were positive until the eighteenth day.

Blood transfusions were given, 100 cc. of blood being given daily for thirteen days; 500 cc. of 0.4 per cent saline solution was administered intravenously daily for seven days. During the first two days lumbar drainage was done every eight hours. Cisternal drainage was carried out daily. Five grains (0.3 Gm.) of sulfanilamide was administered every six hours, and 40 cc. of an 0.8 per cent solution of sulfanilamide was given intrathecally daily. Sulfanilamide was discontinued on the third day. Staphylococcus aureus antitoxin was given in 100 cc. amounts twice daily, and 40 cc. was administered intrathecally for six days.

ORR, Buffalo.

CONVULSIONS IN THE CHRONIC NERVOUS DISEASES OF INFANCY AND CHILDHOOD. ALBERT W. PIGOTT, SAMUEL M. WEINGROW and THOMAS S. P. FITCH, Arch. Pediat. **57:**92 (Feb.) 1940.

A series of articles on this subject has been brought to completion, with the following summary and conclusions.

1. Epilepsy is largely a disease of infancy, childhood and adolescence, since the average age at onset in 1,000 cases was 11.1 years.

2. In a group of 553 classified cases of the 1,000 cases of institutional epilepsy, three groups can strictly be said to belong to the diseases of adult stage. They are alcoholism, of which there were 16 cases; acquired syphilis, found in 18 persons with epilepsy, and cerebral arteriosclerosis, from which eleven persons were suffering.

3. An analysis of the factors causing the epilepsy in these cases is presented.

4. Other procedures essential for diagnosis of this condition are studies of the aura, of the neurologic findings and of the encephalographic as well as the meningographic picture.

5. The work of Penfield in relation to the aura and other preparoxysmal phenomena, as well as the pattern of attack, is emphasized.

6. The material has been divided equally into the sensory and motor auras, as well as groups depending on the lobes of the cerebral hemisphere where the particular trigger zones responsible for these phenomena are located.

7. Neurologic examinations were performed in over 600 of the 1,000 cases presented. Certain factors in gait, attitude, reflexes and sensory and cranial nerves, as revealed by the neurologic examinations, were stressed in the examination of the patients.

8. Encephalographic procedures were carried out for over 300 of the institutional epileptic patients. An analysis of the neurologic findings in relation to the encephalographic findings in 184 patients is given in detail.

9. A discussion of the meningographic procedure and its modifications is presented. This procedure, which was introduced as a subdural procedure by Ney, has been carried out in about 40 patients in whom the encephalographic procedure was also carried out.

10. A comparison is made in some instances between the encephalographic and the meningographic observations; certain advantages of the former as well as those of the latter are cited.

11. The average age at death of a group of 58 persons on whom autopsy was performed is 38.8 years. The observations at autopsy in 58 persons are presented. In almost all instances the premortem and postmortem observations corresponded in regard to the location of the disease in the particular system the involvement of which caused death.

12. The causes of death in 602 persons on whom autopsy was not performed are presented, and the average age at death of the patients who died of the disease, as well as the number of cases in each group, is given.

13. The problems involved in these conditions are sketched, and emphasis is placed on the necessity for continued study of this phase of epilepsy.

14. In the light of the etiologic and encephalographic findings in these institutional cases of epilepsy in relation to the neurophysiologic phenomena connected with the observations at autopsy, it becomes evident that the problems presented concern not only epilepsy but neurologic conditions in general. ORR, Buffalo.

EPILEPSY COMPLICATED BY UNCONTROLLABLE DIABETES MELLITUS. ALEXANDER T. ROSS and WILLARD W. DICKERSON, Endocrinology **27**:200 (Aug.) 1940.

Two cases of uncontrollable juvenile diabetes mellitus with epilepsy are presented. Each condition apparently was a separate entity. JACOBSEN, Buffalo.

PERIODIC PARALYSIS. A. D. M. KRAUS, Illinois M. J. **77**:371 (April) 1940.

The knowledge of periodic paralysis is reviewed, and a case report is given.

BARBOUR, Peoria, Ill.

VENTRICULAR DILATATION IN SPINA BIFIDA. B. SHAPIRO and V. G. TOSTI, J. Pediat. **16**:318 (March) 1940.

Ventriculograms were made for 6 infants with spina bifida and meningocele or myelocele prior to operative intervention anywhere from the fifth day to the sixth week of life. In each instance some dilatation of the ventricles was found despite the fact that clinically no evidence of hydrocephalus was present. Shapiro and Tosti conclude their report with a discussion of the cause and site of the obstruction giving rise to the dilatation of the ventricles and subsequent hydrocephalus in cases of spina bifida.

RAUH, Cincinnati.

THE HYPERTONIC INFANT. A. TOW, M. Clin. North America **23**:607 (May) 1939.

The picture of the hypertonic infant is familiar. It is known by such symptoms as sleeplessness, hyperactivity of the muscular system, marked nervous instability, vomiting and capricious reactions to food. This syndrome is due to an autonomic imbalance caused by hyperactivity of the vagus nervous system. The vagus and sympathetic systems are antagonistic. When one contracts, the other dilates; hence the almost specific action of atropine in treatment. Phenobarbital, the action of which is probably central, is of great value in conjunction with atropine. The action of atropine is short lived. It is important to give the drug just before feeding instead of fifteen minutes before, as often recommended. The initial dose should be small, 1/1,000 grain (0.000065 Gm.) or less; the dose is then carefully increased until a clinical or physiologic response is obtained. Atropine is

best given in tablet form, since solutions deteriorate rapidly on standing. Phenobarbital is best given as the soluble sodium salt. One-eighth grain (0.008 Gm.) two or three times a day is usually sufficient. EUGENE H. SMITH, Ogden, Utah.

ELECTROENCEPHALOGRAPHIC STUDIES IN RELATIVES OF EPILEPTICS. H. STRAUSS, W. E. RAHM JR. and S. E. BARRERA, Proc. Soc. Exper. Biol. & Med. **42**: 207 (Oct.) 1939.

Electroencephalograms were made for 93 relatives of 31 epileptic patients. They disclosed three types of tracings: abnormal (between 3 and 6 cycles per second of an amplitude of at least 50 microvolts), suspicious (a similar series of low amplitude or similar slow frequencies in relatively large numbers but not forming series) and normal (showing none of these characteristics). It was found that 23 per cent of the parents and 28 per cent of the siblings had definitely abnormal tracings. One group of families had a high incidence of abnormal electroencephalographic findings, while the other had no such abnormalities. These findings are being studied from the practical, genetic and therapeutic angles, as well as from the diagnostic and prognostic points of view. HANSEN, Minneapolis.

THE CAUSE OF THE REDUCTION OF THE SUGAR CONTENT OF THE CEREBROSPINAL FLUID IN MENINGITIS. E. HENDRY, Arch. Dis. Childhood **14**:307 (Dec.) 1939.

The permeability of the choroid plexus to dextrose is not affected in cases of meningitis. The reduction in the cerebrospinal fluid sugar in meningitis is due to glycolysis within the cerebrospinal system. The presence of the meningococcus or of the tubercle bacillus in the spinal fluid is not responsible for the reduction in the latter's sugar content in meningitis due to these organisms. Bacillus coli has a glycolytic action, and in coliform meningitis the reduction in cerebrospinal fluid sugar is in great part due to this. Polymorphonuclear leukocytes possess powers of glycolysis, and their presence supplies the reason for the reduction in cerebrospinal fluid sugar content in tuberculous meningitis. KELLY, Milwaukee.

PHYSIOTHERAPY IN NERVE AFFECTIONS. M. F. FORRESTER-BROWN, Brit. J. Phys. Med. **2**:98 (April) 1939.

The author discusses the use of hydrotherapy, dry heat, irradiation, cold air, electrical stimulation, massage, exercise, manipulation and occupational therapy in combating various nerve involvements. He believes that the role of physical therapy is as follows: (1) to improve the circulation, (2) to render and maintain joints over which the patient has lost control in a mobile condition, (3) to restore the patient's confidence in himself and (4) to increase the patient's activities steadily and gradually. HARTMAN, Cleveland.

CEREBRAL HAEMORRHAGE FROM RUPTURE OF A CONGENITAL INTRACEREBRAL ANEURYSM IN A CHILD. K. HERMANN and A. R. MACGREGOR, Brit. M. J. **1**:523 (March 30) 1940.

The report of this case ends with a discussion of "acute cerebral vascular catastrophies" in young people. Under etiology one finds that "aneurysms of the cerebral arteries may be congenital, arteriosclerotic, or mycotic. It is now recognized that the majority of them are congenital." Embryologic and anatomic effects are discussed. Arteriosclerotic aneurysms are practically ruled out. In the case reported, the patient was admitted in an unconscious state. He had "interrupted his play spontaneously and abruptly, sat down and complained that his left ear was painful. Presently he collapsed and 'seemed to shake.' His right eye was observed to turn outwards." Shortly after admission to the hospital respiration was suspended. The child died after insertion of a tracheal tube. A cisternal puncture was performed and showed fluid blood and other evidences of hemorrhage.

At postmortem examination there was found extensive hemorrhage into the substance of the left frontal lobe from a ruptured aneurysm embedded in the anterior part of the medial wall. The diagnosis was aneurysm of developmental origin.

ROYSTER, University, Va.

MIGRAINE IN PEDIATRIC PRACTICE. R. LIÈGE, Progrès méd. **68**:25 (Jan. 6) 1940.

This discussion of migraine in the child stresses again the hereditary factor. The symptoms differ from those in the adult in that the headache is not so likely to be unilateral. Differentiation from acetonuric vomiting is sometimes difficult but not significant with respect to therapy. More important is the ruling out of appendicitis and the meningitides, and suggestive symptoms should not be dismissed without examination. In treatment of an attack, the author uses antipyrine and chloral hydrate in the form of a suppository. In general, he advises moderation in intellectual work, frequent recreation and long vacations in the country. If allergy is a factor, subcutaneous injections of 5 per cent peptone or intravenous injections of 20 per cent sodium hyposulfite or of calcium may be of value.

LESLIE, Evanston, Ill.

HYDROCEPHALUS WITH UNUSUAL SYMPTOMS. K. GREINER, Orvosi hetil. **83**:971 (Nov. 4) 1939.

A 19 month old boy showed *coniugation deviée* and paralysis of the bladder after angina of short duration. The patellar and achilles reflexes were diminished. The cerebrospinal fluid was normal, but encephalographic examination revealed internal hydrocephalus, which seemed to be of earlier origin. After systematic lumbar punctures, the neurologic symptoms disappeared quickly. Greiner expresses the belief that the latent hydrocephalus became manifest because of increased production of the cerebrospinal fluid caused by angina.

GÖTTCHE, Budapest, Hungary.

CONTINUOUS IRRIGATION OF THE SPINAL FLUID FOR MENINGITIS OF OTITIC ORIGIN. K. SHIMIZU, Ztschr. f. oto-rhino-laryng. **45**:381 (March) 1939.

In a 10 year old boy acute meningitis developed as a complication of chronic mastoiditis of several years' duration. The spinal fluid gave strongly positive Nonne-Apelt and Pandy reactions. It contained 2,201 cells, mostly polymorphonuclear, though culture did not show growth, and Queckenstedt's sign also was negative.

On the evening of the boy's admission to the hospital radical mastoidectomy was performed. This was followed by continuous irrigation of the spinal fluid. For hydration the patient received 700 cc. daily of Locke's solution, both subcutaneously and intravenously, in addition to methenamine, 4 Gm. daily, in the vein. After this treatment the signs of meningeal irritation gradually subsided, and on the seventeenth postoperative day spinal irrigation was suspended. With the reappearance of untoward signs the irrigation was reestablished and continued until the cell counts became normal, which occurred on the fifty-seventh postoperative day. The patient was dismissed on the seventy-third postoperative day. The irrigations were interrupted twice, for five and for three days, during the observation. The average amount of spinal fluid removed daily was 312 cc.; the total in forty-six days was 14,350 cc.

HARA, Los Angeles. [ARCH. OTOLARYNG.]

TREATMENT OF CHOREA MINOR WITH PHENOBARBITAL U. S. P. P. DRUCKER, Acta pædiat. **24**:440, 1939.

Forty-eight children aged 6 to 14 years were treated with phenobarbital U. S. P. Large initial doses were given for two weeks or until an exanthem had appeared, then decreasing doses. Clinical recovery was obtained in all—in half of the group

within two weeks and in three quarters within three weeks. A rash appeared in 17 of the children; it was accompanied by fever in 16. A transient mild relapse was observed in 5 children. No serious complications occurred.

McCune, New York.

Psychology and Psychiatry

The Mentally Handicapped Child. A. S. Hershfield, Illinois M. J. **77**:369 (April) 1940.

The key to the successful education of the mentally handicapped child is patient skilful training under such favorable environment as is afforded by colonization. All who can should talk with the local state senator or representative to support legislation fostered by the committee for the study of mentally handicapped children, to enable the building of the cottage system of colonies for the teachable feebleminded.

Barbour, Peoria, Ill.

Genital and Sphincter Behavior of the Male Infant. H. M. Halverson, J. Gen. Psychol., March 1940, p. 55.

Little information is available on the genital and sphincteric behavior of infants. This study was undertaken to learn the frequency of penial tumescence and its relation to other forms of infantile behavior, particularly micturition and defecation. The subjects of this study were 9 male infants varying in age from 3 to 20 weeks. The period of observation covered ten days. Each day's observation was continuous and extended from 8:30 a. m. until 5 p. m.

It was found that penial tumescence was a common occurrence for all infants. There was marked individual variability in its frequency and duration. It occurred during sleep as well as during wakefulness. In general, behavior during tumescence was characterized by various signs of restlessness. Such activity as repeated reaching for the penis and scrotum and grasping and clawing the genitals violently left no doubt as to the source of the discomfort which tumescence occasionally induced. Situations most likely to produce tumescence were micturition, defecation and waiting for the bottle.

The frequency and times of the day when micturition and defecation were most likely to occur were determined for these infants. Among other things it was found that there was little associative behavior during these excretory acts. However, general restlessness usually preceded the act. The majority of micturitions and about one-half the defecations were associated with varying degrees of penial tumescence.

The author concludes that pressure stimulation of the bladder is the most probable cause of tumescence, since there is a close relation between voidings and tumescence, with the occurrence of detumescence after micturition has been completed. He believes that fecal pressure in the colon and rectum directed against the bladder probably accounts for the frequent voidings and the presence of tumescence at defecation. He feels that tumescence tends to prevent voiding and that the greater the turgidity of the penis the greater the interference with voidings.

Weinfeld, Highland Park, Ill.

Anodontia in Mongolism. D. H. H. Thomas, J. Ment. Sc. **85**:566 (May) 1939.

Anodontia, the complete absence of teeth, both milk and permanent, is a rare condition. Thomas reports the case of a female mongolian idiot aged 61 who had complete anodontia of both the first and the second dentition. Thomas points out that both anodontia and mongolism are due to a developmental defect in the ectoderm, and that possibly both appear in the same period of ontiogenetic development.

Kasanin, San Francisco. [Arch. Neurol. & Psychiat.]

TWENTY YEARS OF CHILD PSYCHIATRY. MARY CHADWICK, Ztschr. f. Kinderpsychiat. **6**:175 (March) 1940.

This article does not lend itself to abstracting.

JAHR, Omaha.

THE CHILD WITHIN THE FAMILY. WILLIAM STERN, Ztschr. f. Kinderpsychiat. **7**:6 (May) 1940.

The importance of considering the child as a distinct individual of the family as an institution is stressed. The author remarks that as a human being the child has received a good deal of attention in the sociologic sphere but that his status in the home has been overlooked to a large degree. Yet there is no phase of life in the domestic haven which for better or for worse does not leave its impress on the mind of the youngster. Religion, politics, economics, social standing, cultural state and moral codes all reflect themselves in the development and disposition of the growing organism.

Individual problems confronting the child in the home, such as his constellation among his siblings, his mental capacities in meeting competition, his physical advantages or disadvantages in commanding attention from others and many other personal factors influencing his rank and dignity are discussed in detail.

JAHR, Omaha.

INFANTILE SCHIZOPHRENIA. R. VEDDER, Maandschr. v. kindergeneesk. **9**:352 (June) 1940.

Vedder gives a description of the symptoms of infantile schizophrenia. In childhood dementia praecox shows two different types, one type occurring in children under the age of 6 years and the other in the school child. The older the child, the greater the resemblance of the symptoms to those of the disease occurring in adults. In cases of quick aggravation, complete dementia soon develops; in those with a slower course there are more disturbances in the way of thinking and feeling, but in all cases a distinct rupture between the child and its outer world is present. A discussion is added of the question whether the dementia infantilis of Heller is a form of infantile schizophrenia; the author is inclined to answer this question in the affirmative. Experience has taught that the prognosis of infantile schizophrenia is bad; modern therapy has not yet given favorable results.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

RENAL FUNCTION AS A FACTOR IN THE URINARY EXCRETION OF ASCORBIC ACID. J. SENDROY JR. and B. F. MILLER, J. Clin. Investigation **18**:135 (Jan.) 1939.

Abnormally slow excretion of administered ascorbic acid does not necessarily indicate a low ascorbic acid content of the body when real function is low, because renal damage retards excretion even when no deficit in ascorbic acid exists. The effect of impairment of renal function on the clearance of ascorbic acid runs approximately parallel to the effect on the urea clearance.

GUEST, Cincinnati.

TREATMENT OF CRYPTORCHIDISM WITH MALE SEX HORMONE. C. ZELSON and E. STEINITZ, J. Pediat. **15**:522 (Oct.) 1939.

Twenty boys between the ages of 7½ and 13 years with undescended testicles were treated with testosterone propionate. In 17 of the boys the condition was unilateral and in 3 bilateral. Eleven had been previously treated with a gonadotropic substance, without effect. Of these 11 boys, 2 responded to the testosterone propionate treatment. There was complete descent in 3, 15 per cent of the entire group. Testosterone propionate had a partial effect on some of the other children:

in 5 the testicles came down to the lower end of the canal; in 4 the testicles became palpable in the canal; in 16 the penis became enlarged, in 8 enlargement of the scrotum followed treatment, and a definite growth of pubic hair occurred in 10. In 5 the testicles became smaller during the treatment. Four of the children who had not responded to treatment with testosterone propionate alone were given a second course of treatment in which a gonadotropin was used with testosterone propionate. Two of these children responded with complete descent of the testicles. One child with bilateral cryptorchidism who failed to respond to testosterone propionate was subsequently given 10,000 units of a gonadotropin, with resultant complete descent of the testicle. The authors conclude that gonadotropin is more effective than testosterone in the treatment of cryptorchidism. Some conditions which do not respond to gonadotropin alone will respond to combined treatment with testosterone and gonadotropin.

RAUH, Cincinnati.

SPONTANEOUS ERECTIONS IN EARLY CHILDHOOD. J. H. CONN and L. KANNER, J. Pediat. **16**:337 (March) 1940.

Little information is available in the literature concerning penile erections in early childhood not associated with masturbation. The parents of 128 boys were asked whether erections had ever been noticed and, if so, the ages at which they began, the circumstances under which they occurred, and the period of time during which they continued. In 47 (36.7 per cent) of the 128 boys, spontaneous erections were seen. Thirty-eight boys were reported as beginning to have erections during the first five years of life. The earliest observation was traced to 2 months of age. Two children were observed to have erections at 6 months. Seven began to have erections in the second half of the first year. Twelve boys had erections for a limited time only; the others continued having them up to the time of investigation. Twelve boys had erections coincident with fulness of the bladder on awakening in the morning or associated with urinary urges. One child was seen to have erections during sleep. In only 1 child did sex preoccupations seem to play a significant part. No correlation could be established between erections and inflammatory or other penile disorders. The average intelligence quotient for the group was 94. Nineteen of the boys (40.4 per cent) also gave histories of masturbation in the past or at the time of inquiry.

RAUH, Cincinnati.

OBSTRUCTIONS OF THE VESICAL NECK IN CHILDREN. R. W. MCKAY, South. M. J. **33**:377 (April) 1940.

McKay states that tremendous advances have been made in recent years by urologists in the diagnosis and treatment of obstruction of the bladder neck in children except when it is due to sarcoma, in the treatment of which little has been accomplished. The transurethral methods are the methods of choice in removing obstructions.

If the child with such a condition is really to benefit, physicians as a group, especially pediatricians, should be on the watch for obstructions, as the earlier an obstruction is removed, the better chance the child has to make a complete recovery.

SCHLUTZ, Chicago.

RESULTS OF UNTREATED UROLOGIC CONDITIONS IN CHILDHOOD. J. E. GLENN, South. M. J. **33**:388 (April) 1940.

Glenn believes that some urologic conditions in children are not treated because they are not recognized. The medical profession and the laity should be better informed as to how these conditions are best recognized and treated. As the recognition of urologic conditions in children increases, the incidence of adult urologic disease will decrease. Every child should have a urinalysis at least once each year.

SCHLUTZ, Chicago.

NOCTURNAL ENURESIS. D. M. ODLUM, Brit. M. J. **1**:8 (Jan. 6) 1940.

Enuresis, both diurnal and nocturnal, is discussed along more or less conventional lines. Various etiologic factors are outlined and discussed, and suggestions are made for the control and remediation of the condition.

ROYSTER, University, Va.

TREATMENT OF ACUTE LOCALIZED SUPPURATIVE MASTITIS WITH A PROTEOLYTIC ANTIFERMENT. D. MARAGLIANO, Med. inf., Rome **10**:334 (Nov.) 1939.

Maragliano has had success in treating localized suppurative mastitis by injections of proteolytic antiferments and has thus avoided the necessity of surgical intervention.

HIGGINS, Boston.

Diseases of the Ductless Glands; Endocrinology

SOME EFFECT OF THYMUS REMOVAL IN CHICKENS. G. H. MAUGHAN, Am. J. Physiol. **123**:319 (Aug.) 1938.

Removing the thymuses from growing chickens produced no significant differences in the rate of growth of the chickens as compared with that of controls. Experimental rickets developed at the same time and reached the same degree of severity in control and in thymectomized chickens. There was no demonstrable difference in the level or in the utilization of calcium.

NOURSE, Cleveland.

DIFFERENTIAL DIAGNOSIS OF BASOPHILISM AND ALLIED CONDITIONS. RALPH I. DORFMAN, HUGH M. WILSON and JOHN P. PETERS, Endocrinology **27**:1 (July) 1940.

The authors report 15 cases of a syndrome characterized by obesity confined to the face and trunk, redness of the face, cyanotic striae distensae over the trunk, ecchymoses on the lower extremities and acneform eruptions. In females there are also amenorrhea, drying and thinning of the hair on the head and hirsutism of the face and trunk. In the male sexual powers may be impaired. In addition, the blood pressure becomes elevated, and eventually arterial changes of the malignant nephrosclerotic type are found. In a large proportion of patients, but not in all, carbohydrate tolerance is impaired. Osteoporosis, especially affecting the spine, is common.

The patients have been found to have one of three conditions: (1) basophilic adenomas of the pituitary, (2) hyperplasia or tumors of the adrenal cortex or (3) solid tumors of the ovary, arrhenoblastomas. An attempt is made to find criteria by which these may be distinguished from one another: arrhenoblastomas are seldom if ever attended by the circulatory or metabolic disorders which usually characterize the two other conditions. True virilism seems to occur only with adrenal cortical tumors or hyperplasia and with arrhenoblastoma. In the former conditions the urine contains excessive amounts of materials having androgenic activity. If the condition appears before growth is completed corticoadrenalism gives rise to precocious development and precocious union of the epiphyses, while in basophilism development and epiphysial union appear to be retarded. In no cases of this series in which it was measured did urinary estrogenic activity exceed normal limits.

JACOBSEN, Buffalo.

CELLULAR CHANGES IN THE ANTERIOR PITUITARY GLAND OF RATS WITH EXPERIMENTAL GOITER. GEORGE R. SHARPLESS and ELIZABETH M. HOPSON, Endocrinology **27**:129 (July) 1940.

That cellular changes occur in the anterior lobe of the pituitary as a result of dysfunction of the thyroid is an established fact. In this paper the authors are concerned with the changes in the pituitaries of rats with experimental goiter.

Rats fed a goiter-producing soy bean diet showed changes in the anterior lobe of the pituitary similar to those found in thyroidectomized animals, that is, decreased proportion of acidophils, increased proportion of basophils and formation of colloid-like vacuoles in the basophils. Iodine or desiccated thyroid caused a significant decrease in the size of the pituitary. Animals fed the soy bean diets had a lower percentage of acidophils than did normal controls. It is suggested that this is related to the subnormal rate of growth. Iodine or desiccated thyroid increased the proportion of acidophils and decreased the proportion of basophils, but only desiccated thyroid produced the normal percentage of basophils.

JACOBSEN, Buffalo.

THE EFFECT OF PITUITARY PREPARATIONS ON THE TOTAL BODY GLYCOGEN, WATER, NITROGEN AND FAT OF MICE. A. H. NEUFELD, S. M. SCOGGAN and G. S. STEWART, Endocrinology **27**:132 (July) 1940.

This investigation was undertaken to elucidate the relation of the pituitary body to the metabolism of carbohydrates, proteins and fats.

Evidence is presented to show that certain anterior pituitary preparations, on administration to normal fasting mice, produce an appreciable rise in total body glycogen, associated with a low content of fatty acids.

JACOBSEN, Buffalo.

ASSOCIATION OF ADRENAL CORTICAL INSUFFICIENCY AND LACK OF VITAMIN C. A. GIROUD and A. R. RATSIMAMANGA, Presse méd. **48**:449 (May 1-4) 1940.

Many authors have noted that the early signs of scurvy parallel those of adrenal cortical deficiency. It has been shown that there is a high concentration of ascorbic acid in the normal adrenal cortex. Scurvy produced in a guinea pig is first characterized by fatigability, muscular atrophy, apathy, and edema. These symptoms can be made to disappear by the injection of extract of adrenal cortex. The hemorrhagic lesions and the changes in the bones and teeth are not affected by the extract. Changes in the blood chemistry seem identical in the two conditions. In scurvy the adrenals become much enlarged in direct relation to the amount of ascorbic acid present.

The authors suggest that these facts be taken into consideration in the prophylaxis and treatment of conditions showing any symptoms of adrenal cortical deficiency. The addition of ascorbic acid to the therapeutic measures used for Addison's disease, myasthenia gravis and amyotrophic lateral sclerosis seems definitely indicated.

DAFFINEE, Boston.

SUPERIORITY OF THE PNEUMOMEDIASTINAL METHOD FOR THE DIAGNOSIS OF ATYPICAL FORMS OF HYPERTROPHIED THYMUS. R. PEREIRAS and A. CASTELLANOS, Arch. de med. inf. **8**:327 (Sept.) 1938.

Pereiras and Castellanos do not believe that many forms of hypertrophied thymus can be distinguished by means of the ordinary anterior-posterior or lateral roentgenogram. They employ the method of Condorelli (*Minerva med.* **28**:81, 1936) as a means of diagnosis. This consists in injecting air or oxygen into the mediastinum and then taking roentgenograms. They consider this method to be harmless, even in the first month of life. By the use of this method they are enabled to describe a form of thymic hypertrophy not before mentioned in the literature, which they designate as "vascular." In this form the lobes of the thymus are located within the vascular pedicle, so that they appear hidden behind the sternovertebral shadow. This is an excellent article, with 44 illustrated pictures of the mediastinum at various angles. It should be read in full by those interested.

SANFORD, Chicago.

EFFECT OF INHALATION OF CARBON MONOXIDE ON THE THYROID GLAND. H. REPLOH, Arch. f. Hyg. **120**:244, 1938.

Studies were carried out on rabbits and guinea pigs. However, only guinea pigs were used as subjects for acute and subacute poisoning. In acute poisoning the colloid was changed in color. Vacuoles appeared. A few follicles were free from colloid, and congestion was increased. In subacute poisoning (the animals receiving repeated short exposures to high concentration of the gas) the changes were more marked, with greater epithelial proliferation. With longer periods of inhalation, up to six hours daily for six to thirty weeks, and slight concentrations, colloid diminished and epithelial proliferation increased. Over longer periods, up to a year, the principal additional change was an increase in interstitial tissue, especially in connective tissue. The same picture appeared more rapidly, within four months, if acute was followed by chronic poisoning. These observations are in agreement with previously published studies. Somewhat similar results may be obtained by feeding the animals thyroid.

GLASER, Rochester, N. Y.

HYPOGLYCEMIC PHASES IN JUVENILE DIABETES MELLITUS. G. PISAROVIC, Časop. lék. česk. **75**:936 (July 17) 1936.

Hypoglycemia usually appears two to six hours after an injection of insulin but may appear in twenty to thirty minutes. The differentiation from hyperglycemia may be made as follows: 1. The urine is usually sugar free though at times glycosuria and even ketonuria may be present. 2. The level of the blood sugar is variable but usually is lower than when the child has no symptoms. 3. The history of the diet within the past twenty-four hours and notation of recent exertion may afford evidence. 4. An intravenous injection of dextrose clears up the symptoms, whereas in hyperglycemia it has no effect while insulin reduces the symptom.

The marked variability of the sugar content of the blood and the marked tendency to hypoglycemia in juvenile diabetes is explained on the following hypotheses: (1) insufficient correlation of the internal secretory apparatus, (2) lability of the vegetative nervous system, (3) increase in basal metabolism after exertion, (4) inconstancy of the glycogen content of the liver and (5) a simpler mobilization of the endogenous insulin of the juvenile pancreas.

STULIK, Chicago.

SYMPATHOGONIOMA (NEUROBLASTOMA) OF THE ADRENAL IN INFANCY. J. STOLZ and D. KUCERA, Časop. lék. česk. **75**:1148 (Sept. 11) 1936.

The differential diagnosis is difficult and is usually made at autopsy except in cases in which a metastasis lends itself to biopsy. Metastases spread through both the lymph and the blood stream and especially to the orbit and cranial bones and to the liver. In a review of the literature Herxheimer collected 29 cases. This report cites a girl of 9 months with a history of prolonged fever, anemia and enlargement of the abdomen (49 cm. in circumference) with a nontender palpable tumor extending into the left costovertebral area. The autopsy and the histologic observations are given in detail.

STULIK, Chicago.

NEUROBLASTOMA OF THE ADRENALS. E. VERMAAS, Maandschr. v. kindergeneesk. **9**:111 (Dec.) 1939.

Vermaas presents a description of a case of neuroblastoma in a girl nearly 3 years old, with metastatic tumors in the skull (Hutchinson type) and in the liver (Pepper type). The diagnostic importance of puncture of the sternal marrow is indicated, in spite of uncertain findings in the beginning.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Muscles, Bones, Joints and Lymph Glands

ACUTE OSTEOMYELITIS WITH STAPHYLOCOCCEMIA. L. D. BAKER and A. R. SHANDS, J. A. M. A. **113**:2119 (Dec. 9) 1939.

The authors review 648 cases of staphylococcic disease, in 103 of which there was septicemia. They compare the results when staphylococcus antitoxin was given and when it was not given. The indications were found in cases of osteomyelitis with septicemia in which the Schilling index showed a shift to the left, an indication of failure of production of immune bodies. Among 49 children with this condition 30 received antitoxin, with 7 deaths, while 10 of 19 without it succumbed. Adequate drainage of the focus is imperative. Reactions were poor.

HEERSMA, Kalamazoo, Mich.

AMYOTONIA CONGENITA (OPPENHEIM'S DISEASE) OCCURRING IN TWO OF TRIPLETS. A. GOURSE, J. Pediat. **15**:546 (Oct.) 1939.

Amyotonia congenita is reported as occurring in identical twins with a triplet but not in the third child. Since one child was normal, Gourse believes that the abnormality underlying this disease was present in the fertilized ovum or in the zygote or that there was a defect in the germ plasma of one or both parents prior to conception. It has been previously reported that amyotonia congenita occurs most frequently in persons whose blood is of type 2. The mother and all three children in this report had blood of type 2. A decreased magnesium content of the red blood cells has also been reported in this disease. Determinations of blood magnesium gave the same values for the twins with amyotonia congenita and the normal triplet.

RAUH, Cincinnati.

STATUS LYMPHATICUS. J. F. TAYLOR, Proc. Roy. Soc. Med. **33**:119 (Dec.) 1939.

Taylor states that for more than two hundred years sudden and unexpected death from trivial causes was thought to be explained by the enlargement or so-called persistence of the thymus. Nearly fifty years ago it was realized that the enlargement of the thymus was only one item in a general lymphoid hyperplasia, which was thought to be indicative of, but not the cause of, some constitutional anomaly. This condition was called status lymphaticus. This general conception seems to have been lost sight of in the repeated investigations made on the variations in the size of the thymus. Attention has been drawn to the association of a large thymus with Addison's disease, the syndrome of exophthalmic goiter and deficiency of the sex organs. One theory advanced in recent times is based on a belief that adrenal insufficiency is the essential factor. Taylor has formed the opinion that subjects showing general lymphoid hyperplasia are more liable to die from trivial causes. He does not see how this is possible of proof, statistical or otherwise, as no one can determine the degree of triviality of a cause. It is obvious that the diagnosis of status lymphaticus can be, and maybe is, abused in that it may be used to cover up a blunder or to conceal ignorance, but this applies to any form of dishonesty. He says: "I cannot think this happens often. The anaesthetist who turns on the carbon dioxide instead of the oxygen or the surgeon who cuts the aorta is not likely, I think, to be shielded by the pathologist who sees the picture of status lymphaticus with the eye of faith or friendship. I cannot feel, however, that any harm can be done if it is mentioned that a lymphatic condition is present, even if its exact meaning is not understood, in cases where there is no other obvious cause of death. If the terms 'status thymico-lymphaticus' and 'thymic death' were abandoned and the simple term 'lymphatism' used instead, there would be less misconception, and observations on these cases might be better directed and possibly lead to some solution of the problem, which certainly does still exist."

WILLIAMSON, New Orleans.

COMPOSITION OF BONE IN EXTREME OSTEOPOROSIS ASSOCIATED WITH HEPATOMA. A. E. HANSEN, L. S. PALMER and J. W. NELSON, Proc. Soc. Exper. Biol. & Med. **43**:206 (Jan.) 1940.

This report deals with the results of extensive mineral analyses of green, dry and dry extracted bone from a 10 year old boy having extreme decalcification of the entire osseous system associated with primary carcinoma of the liver of at least two years' duration. There was marked replacement of bone minerals by lipid and water, amounting to 27.8 per cent, based on analyses of bone from a control subject with normal skeletal structure. Slightly more than 80 per cent of this was lipid (alcohol-ether soluble) material. The dry, lipid-free bone from this child with the hepatoma had 31.4 per cent less calcium, 33.8 per cent less phosphorus, 39 per cent less magnesium and 37.9 per cent less carbon dioxide than that of the control. Based on the system of calculation used, relatively more calcium carbonate and magnesium phosphate than calcium phosphate was withdrawn from the bone. The ratio of calcium phosphate to calcium carbonate was 6.918, as compared with 6.471 for the control subject, a finding which seems significant in that this ratio decreases in rickets, osteomalacia and phosphorus deficiency. Therefore, the bone abnormality in this child with the hepatoma is more analogous to calcium deficiency than to either vitamin D or phosphorus deficiency.

FROM AUTHORS' SUMMARY (HANSEN, Minneapolis).

HODGKIN'S DISEASE. C. BAKER and W. N. MANN, Lancet **1**:23 (Jan. 6) 1940.

The observations are based on 65 cases of Hodgkin's disease seen at Guy's Hospital between 1926 and 1937. The clinical diagnosis was confirmed by biopsy or autopsy. Tuberculosis is neither a factor in the causation of the disease nor a common association.

Cure was effected in 2 cases by surgical excision of glands followed by treatment with roentgen rays of high voltage. It is suggested that more patients might be cured if this treatment were used early. LANGMANN, New York.

Diseases of the Eye

CORNEAL INVOLVEMENT IN CONGENITAL ICHTHYOSIS (KERATODERMA). DERRICK VAIL, Arch. Ophth. **24**:215 (July) 1940.

An unusual case of marked photophobia, lacrimation and white, circumscribed, elevated nodes of the cornea in association with congenital ichthyosis is reported. Removal of the nodes and large doses of vitamins A and D gave marked relief.

WESCOTT, Chicago.

MANIFESTATIONS OF TUBERCULOSIS IN OPHTHALMIC PRACTICE. H. M. TRAQUAIR, Edinburgh M. J. **47**:57 (Jan.) 1940.

Traquair discusses the two types of tuberculosis of the eye: allergic reaction and tubercle bacillus infection. In describing the ophthalmia he uses the term "scrofulous" in preference to "phlyctenular" because of the association of the ocular condition with scrofula and cervical adenitis. This is one of the more common manifestations of the allergic type of ocular tuberculosis and is expressed in chronic photophobia, blepharospasm and lacrimation (especially if the cornea is involved). The typical lesion is the phlyctena, which is an accumulation of round cells at the corneoscleral junction, sometimes in the lower outer quadrant. When the involvement is severe, the ulcerative lesion extends into the cornea, and may be followed by pannus of the whole surface. Perforation and prolapse of the iris may occur, but it is rare for vision to be entirely lost or for the eye to be destroyed. During the year 1925 a survey of 3,300 school children showed that 7.3 per cent had been affected with scrofulous ophthalmia. The lesion is not so

common as thirty years ago, owing to the general improvement in hygiene and body welfare. It is still an important disease, and the present opinion favors tuberculosis as the chief factor in the causation.

In 1936 testing showed that 80 per cent of these patients reacted to tuberculin positively as opposed to 20 per cent of the controls. The phlyctena is characteristically a nonspecific response in a person who is sensitive to tuberculin.

The remainder of the article deals with scleritis, another manifestation of allergy, and with other tuberculous infections of the eye. Lupus of the skin may proceed to scarring and ectropion. The author states that tubercle of the eye is as much tuberculosis as tubercle of the lung, and just as resistant to treatment with drops and lotions as pulmonary tubercle would be to sprays and bronchial injections.

NEFF, Kansas City, Mo.

CONGENITAL ABSENCE OF TEARS. W. J. B. RIDDELL, Glasgow M. J. **15**:85 (March) 1940.

The author presents the case of a 5 year old girl who had never shed tears. There was no evidence of keratitis sicca or any other disturbing feature as a result of this malformation. It is thought to be a manifestation of hereditary ectodermal dysplasia.

SNELLING, Toronto, Canada.

RELATIONSHIP BETWEEN PROGRESSIVE FAMILIAL MACULAR DEGENERATION AND PIGMENTARY DEGENERATION OF THE RETINA. R. MUROMATO, Ann. d'ocul. **176**:323 (April) 1939.

Bilateral primary degeneration of the retina was present in 3 brothers and sisters whose parents were second cousins. On clinical examination, 2 of them presented progressive familial degeneration of Stargardt. An ophthalmoscopic examination of the fundi and a functional experiment carried out on the third patient revealed symptoms of pigmentary degeneration of the retina. It was not possible to determine whether the changes in the fundi were caused by diffuse progressive macular degeneration which was gradually spreading or whether they extended throughout the retina at the onset. According to Muromato, progressive macular degeneration of Stargardt and pigmentary degeneration of the retina had caused primary degeneration of the external layer of the retina. Muromato believes that these two diseases are closely associated, but that the localization of the retinal degeneration varies.

BERENS, New York. [ARCH. NEUROL. & PSYCHIAT.]

FETAL KERATOMALACIA. H. D. BOUMAN and S. VAN CREVELD, Maandschr. v. kindergeneesk. **9**:343 (June) 1940.

A mother 16 years old who during pregnancy had used a very deficient diet, especially as regards its content of vitamins, bore a baby who showed congenital changes in the eyes which may be regarded as the consequence of fetal keratomalacia. The authors add a discussion of the recent literature on the effect of shortage of vitamin A during fetal life.

VAN CREVELD, Amsterdam, Netherlands.

Skin Diseases; Allergy

THE FALLIBILITY OF THE AUTOPASSIVE TRANSFER TEST (COWIE). SAMUEL MARTON, J. Allergy **11**:266 (March) 1940.

This is an effort to corroborate Cowie's work. Eight men and 7 women were used in the study; they ranged from 18 to 45 years of age.

The author concludes as follows: The skin of an allergic person which fails to react to specific allergen cannot be passively sensitized with his own serum

(autopassive transfer); the skin of an allergic person which reacts to specific allergen by direct tests shows a 22 per cent drop in positive reactions with autopassive transfer, indicating an inhibitory rather than an enhancing influence.

HOYER, Cincinnati.

EPINEPHRINE HYPERSENSITIVITY: REPORT OF TWO CASES. ARMAND E. COHEN and M. L. WATERSTONE, J. Allergy **11**:393 (May) 1940.

Tissue sensitivity to epinephrine occurred in 2 adult Negresses; necrotic areas developed wherever epinephrine was injected. The possibility that the reaction may have been due to a preservative or to an antigen from the source of the epinephrine was ruled out by testing with sodium bisulfite, chlorobutanol and beef and pork extracts. Neither patient showed sensitivity to synthetic epinephrine hydrochloride.

HOYER, Cincinnati.

DERMATOMYOSITIS IN CHILDREN. O. G. HAZEL and W. M. HULL, South. M. J. **33**:809 (Aug.) 1940.

The authors report 2 cases of dermatomyositis with fatal termination. The patients presented similar involvement of the skin, muscles and heart. The authors discuss the rationale of adrenal cortex, helium and oxygen, histaminase and fever therapy.

The problem of differential diagnosis is discussed.

The condition is fortunately extremely rare.

No form of treatment seems to be particularly successful.

SCHLUTZ, Chicago.

MONGOLIAN MARKS. K. O. HENCKEL, Rev. méd. latino-am. **15**:760 (April) 1940.

The great majority of mongolian marks are localized in the sacrococcygeal region. Microscopically, they are characterized by the presence of pigmented cells, melanoblasts, in the stratum reticularis. This phenomenon was described in 1883 by Baelz, who encountered them with great regularity in newborn Japanese and called them "mongolian marks."

The incidence of mongolian marks varies widely in different countries and races. For example: In Tucaman, Argentina, they are reported as occurring in 51 per cent of children under the age of 1 year. In Bolivia they have been observed in 16.6 per cent of white persons and in 86.6 per cent of Indians. In North America they are reported occurring in 0.28 per cent of white persons and 30 per cent of Negroes. A full bibliography and two photomicrographs are presented.

DWYER, Kansas City, Mo.

CAN PSORIASIS BE CURED BY RESIDENCE IN THE TROPICS? ROBERT SIMON, München. med. Wchnschr. **87**:288 (March 15) 1940.

The author for some time practiced dermatology in Java. It is generally accepted that psoriasis is less frequent in the tropics than in colder climates. The average incidence in Europe is 6 per cent and in America about 3 per cent. The condition occurs rarely among Negroes and Indians. The incidence among Jews is not greater than among Aryans.

During his stay in Java the author observed 7 cases of psoriasis among 187 full-blooded Europeans in his practice and only 3 cases among 270 patients with Indian or Chinese blood.

From his observations the author concludes that there is a racial factor which determines the prevalence of psoriasis. Food and sunshine are not important factors. White persons with psoriasis are not benefited by residence in the tropics.

BRAHDY, Mount Vernon, N. Y.

INFANTILE ACRODYNIA AND ENCEPHALITIS. B. DYKSTRA, Maandschr. v. kindergeneesk. **9**:292 (April) 1940.

A case of infantile acrodynia in a girl of 4¼ years is described. Her illness was regarded as due to encephalitis, in view of the motor disturbances, the vegetative derangement of central origin and the abnormal composition of the cerebrospinal fluid. In connection with etiology, Debré's theory of alimentary intoxication and the theory of infection by Kuiper, Selter, Boureé and others are briefly discussed. The author concludes that the infective theory is to be preferred at present. Accordingly, infantile acrodynia is regarded as a disease caused by a separate neurotropic virus. Finally, the importance is stressed of the study of factors which increase the predisposition.

VAN CREVELD, Amsterdam, Netherlands.

Surgery and Orthopedics

AN OPERATION FOR THE CORRECTION OF CONGENITAL OVERLAPPING OF FIFTH TOE. WALTER I. GALLAND, Bull. Hosp. Joint Diseases **1**:93 (Oct.) 1940.

The author's particular contribution to operative procedure in such conditions is due to his recognition of the part played by an abnormal webbing of the dorsal skin which tends to pull the toe upward and inward. A Z cut across the web overcomes this deforming influence and also permits access for capsulotomy and tenotomy.

LESLIE, Evanston, Ill.

TRAUMATIC RUPTURE OF THE SPLEEN AND THE STOMACH. MELVIN A. CASBERG, J. A. M. A. **114**:1544 (April 20) 1940.

A 3 year old boy, injured on the left side of the trunk by an automobile, presented evidence of rupture of the spleen, with pain in the left upper abdominal quadrant, shock, anemia, leukocytosis and absence of intra-abdominal air. Complete fragmentation of the spleen and perforation of the stomach were present. Fluids, transfusion, splenectomy and repair of the perforation were followed by recovery.

HEERSMA, Kalamazoo, Mich.

SURGICAL PROCEDURES IN GENERAL PRACTICE. H. J. SEDDON, Brit. M. J. **1**:139 (Jan. 27) 1940.

This article does not lend itself to abstracting. It is somewhat technical, and it requires reading in its entirety to be appreciated.

ROYSTER, University, Va.

PREVENTION OF FOOT DEFORMITIES IN CHILDREN. M. EMSLIE, Lancet **2**:1260 (Dec. 16) 1939.

Examination of 281 toddlers (aged 2 to 4 years) inspected at the Woolwich Toddlers' Clinic gave the following figures: Deflection of the terminal phalanx of the great toe, 80 per cent; incipient valgus at the first metatarsophalangeal joint, 11 per cent; flexion of the interphalangeal joint of the great toe, 10 per cent; rotation of the hallux, 2.4 per cent; incipient hammer toe, 13 per cent; distortion of the middle toes, 22 per cent; the same with overlapping, 4.6 per cent; incurved or incurled fourth and fifth toes, 30 per cent; flattened longitudinal arch, 10 per cent; flattened metatarsal arch, 7 per cent; ingrowing toe nail, 12 per cent, and other soft tissue lesions, 9 per cent.

The author emphasizes the importance of a correctly shaped shoe, i. e., one that follows the anatomic axis of the foot, and also socks that are roomy and of the correct shape.

LANGMANN, New York.

Miscellaneous

FOOD POISONING IN A STATE INSTITUTION. Health News **17**:22 (Feb. 5) 1940.

Ninety-six cases of vomiting and abdominal cramps occurred among 631 inmates in a state institution for adolescent boys and young men. The infection was found to have been due to sodium fluoride, which had, by mistake, been used in a chocolate pudding. The sodium fluoride had been used to kill roaches.

AIKMAN, Rochester, N. Y.

A SURVEY OF PEDIATRICS DURING THE PAST 100 YEARS. ISAAC A. ABT, Illinois M. J. **77**:485 (May) 1940.

This historical survey of pediatrics, particularly in the state of Illinois, does not lend itself well to abstracting. It is well worth reading in its entirety.

BARBOUR, Peoria, Ill.

FREEZING RESEMBLING SPINA VENTOSA. N. I. HEYBROEK, Maandschr. v. kindergeneesk. **9**:453 (Aug.) 1940.

A description is given of a baby aged 11 months who showed swelling of the left foot combined with decalcification and necrosis of the left fifth metatarsal bone. The condition resembled spina ventosa, but the roentgen examination, the clinical course and the anamnesis proved it to be a consequence of freezing.

VAN CREVELD, Amsterdam, Netherlands.

Society Transactions

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

CLEMENT A. SMITH, M.D., *President*

D. MURRAY COWIE, M.D.,† *Secretary*

Eighteenth Annual Meeting, Ann Arbor, Mich., Nov. 24 and 25, 1939

President's Address: Maternal Anesthesia and Fetal Anoxemia in Obstetrics. DR. CLEMENT A. SMITH, Boston.

The factors responsible for asphyxia of the newborn are too numerous to be listed here. Since it is easiest to study those which are quantitatively measurable and since the work of Eastman and his colleagues pointed the way, I have been engaged in investigating the effect of various types of anesthesia on the blood of the mother and the infant at the time the infant should be taking his first breath. A graphic summary of certain results has been prepared to show the oxygen relation of the blood of mother and baby in about 90 deliveries under various anesthetics.

In the arterial and the venous blood of 15 mothers during labor but before anesthesia was administered, a slight lowering of the oxygen capacity and a minor arterial anoxemia were present. It will be recalled that Eastman's observations on the maternal blood during delivery effected without anesthesia were similar to these, while he demonstrated that the arterial blood of the newborn infant, in spite of the elevated oxygen capacity, showed only 10.5 volumes per cent oxygen and the blood returning to the placenta showed 3.3 volumes per cent.

Ether.—The figures for the oxygen content of the blood of mother and child in 21 deliveries under ether anesthesia represent the averages of rather widely scattered data, particularly the determinations for the infants. Thus, the value of 12 volumes per cent for the oxygen content of the infant's arterial blood represents a mean of figures ranging from 16.1 to 3.5 volumes, and the range for the venous blood of the infant was from 8.8 volumes to 0.4 per cent. These wide variations are the result of the interplay of the many factors which influence the delicate balance of circulating oxygen. Nevertheless, the group on whom data were obtained is believed large enough to be representative. One striking effect of ether on the maternal blood is the elevation of the oxygen capacity, a phenomenon recently proved to result from an outpouring of erythrocytes from the spleen. Another is the narrowing of the arteriovenous difference in oxygen content. The situation with regard to the infant appears to be highly satisfactory in comparison with Eastman's determinations, which were previously mentioned. He found that the average oxygen contents of the arterial and the venous blood of infants delivered without anesthesia were 10.5 and 3.3 volumes per cent, respectively, while my averages for babies delivered under ether are 12.0 and 3.3 volumes per cent, respectively.

Nitrogen Monoxide and Oxygen.—In these deliveries, even when an attempt was made to keep the concentration of oxygen always at or above 20 per cent of the total mixture of gas in the mask, it was noted that the mother suffered slight and the infant considerable anoxemia. Values as low as 1.4 volumes per cent for the arterial blood and 0.5 volumes per cent for the venous blood of the infant were encountered. The average oxygen levels for the arterial and venous blood of the infants were 7.0 and 2.1 volumes per cent, respectively.

† Dr. Cowie died on Jan. 7, 1940.

Cyclopropane.—This anesthetic was administered in a concentration of about 15 per cent, with 85 per cent oxygen. In deliveries under cyclopropane the maternal arterial blood was almost completely oxygenated and the arteriovenous difference was slight, less than 1 volume per cent. Simultaneously collected specimens of maternal arterial and venous blood were often indistinguishable. This situation did not arise, as might be supposed, from the large amount of oxygen the patient breathed. This can be proved by examining the arterial and venous blood of a subject who has inhaled a mixture of 80 or 90 per cent oxygen with air for half an hour. The oxygen content of both the arterial and the venous blood will be slightly above average, but not nearly at the levels of the patients anesthetized with cyclopropane. This appears to be a specific effect of cyclopropane, similar to the narrowing of the arteriovenous difference in oxygen content produced by ether. It probably results from a more rapid flow of blood through the tissue consequent to dilatation of the peripheral vessels. That its effect is not entirely fortunate was suggested by the levels of oxygen in the blood of the infants, for, despite the apparent suffusion of the mother's blood with oxygen, the average oxygen level of the infants' arterial blood was 9.2 volumes per cent and of the venous blood 3.6 volumes. These levels were better than those of babies delivered under nitrogen monoxide, but considerably lower than those of the average baby delivered under ether.

I was somewhat surprised by the oxygen levels in 28 deliveries under nitrogen monoxide–oxygen–ether anesthesia. In this method of anesthesia unconsciousness is induced by a supposedly safe mixture of nitrogen monoxide and oxygen and then further relaxation is secured by the addition of ether vapor, rather than by pushing the nitrogen monoxide to the point of encroaching dangerously on the supply of oxygen. Nevertheless, it was noted that the values for oxygen in the blood were almost exactly the same as those for mother and child when the anesthesia was produced with nitrogen monoxide and oxygen. In other words, there seems little to choose between these two methods of anesthesia, at least from the standpoint of oxygen supply.

Summary.—Drop ether seems to be the most satisfactory of the four methods of anesthesia mentioned, from the standpoint of the oxygen supply of the infant. In view of Eastman's work and that of Wilson, Torrey and Johnson, I was surprised that some of those infants with less than 2 volumes per cent oxygen in the arterial blood and less than 1 volume per cent in the venous blood showed no evidence of asphyxia. Apparently the infant can stand a remarkable degree of anoxemia for short intervals without damage. On the other hand, although no severe asphyxia was encountered, several of the babies with apparently satisfactory oxygen levels were apneic for a few minutes. This occurred three times among those delivered under ether. Apnea probably results from the narcotizing effect of the anesthetic gas on the infant's respiratory center, in addition to whatever effects may have been produced by disturbance of the circulating oxygen.

DISCUSSION

DR. PHILIP J. HOWARD, Detroit: The information presented has been helpful and will be of definite benefit in the selection of proper obstetric anesthetics. In the administration of nitrogen monoxide–oxygen mixtures it has seemed difficult, if not impossible, to determine the exact percentages of the two gases breathed by the patient, because the gage attached to the gas apparatus does not give a true picture of the composition of the mixture of gases rebreathed from the bag. While the gage may show 12 to 15 per cent oxygen and 88 to 85 per cent nitrogen monoxide, the actual oxygen content of the mixture breathed is often enough lower than this reading to cause deep cyanosis. Cyanosis in the patient is the best guide at present to the actual percentage of oxygen available; analyses of the gas in the mask would be helpful, if it were practical to obtain them.

Occasionally, in order to delay as long as possible the threatened premature onset of labor, large doses of sedatives, such as morphine, must be given. In such

cases the infant is not infrequently born under rather deep sedation and is cyanotic. The question of what stimulation and which method of handling is best for this type of anoxia is of general interest.

DR. N. R. KRETZSCHMAR, Ann Arbor, Mich.: This effort to obtain some concrete data concerning anoxemia and asphyxia of the newborn represents a distinct advance in the study of this problem. Certainly, the reduction of the oxygen content of the blood of infants delivered under nitrogen monoxide should lead one to question the advisability of using this anesthetic agent. However, the fact that many of the babies who had a low oxygen content of the blood were not apneic, while some of those with a high oxygen content were, leads one to suspect that the other factors involved may be more important in the production of asphyxia than is reduction in the oxygen content of the blood caused by the anesthetic administered during the second stage of labor. Important among the factors which must be considered are the analgesics administered during the first stage of labor, with their effect on the intrauterine respiratory movements, and the character of the delivery, with particular reference to intracranial trauma.

DR. K. LOWENBERG-SHARENBERG, Ann Arbor, Mich.: In cases in which death is caused by the use of nitrogen monoxide, there are no signs of anoxemia and death occurs suddenly and without warning. The histologic changes observed in such cases consist of severe, mostly laminar, degeneration of the gray matter. The destruction is distributed rather evenly throughout the cortex and frequently involves the basal ganglions also, though to a much less degree than the brain stem, especially the respiratory area. This histologic picture differs fundamentally from that characteristic of anoxemia and cannot be produced experimentally in animals. All evidence points toward idiosyncrasy as the cause of deaths from nitrogen monoxide anesthesia.

Role of Blood-Clotting Anomalies in the Hemorrhagic Diseases. DR. JOHN H. FERGUSON and MRS. BETTY NIMS ERICKSON, Ann Arbor, Mich.

There are positive causes of bleeding in addition to the negative cause, failure to control the escape of blood. Among the causes are injuries and factors relating to capillary fragility, exemplified in such diseases as scurvy and thrombocytopenic purpura. While the platelets are a possible source of clotting factors, the normal clotting time in cases of thrombocytopenia suggests that the cause of bleeding in such cases must be other than a clotting anomaly. The answer may lie in the decreased capillary resistance and the mechanical failure of thrombus formation.

The fundamental processes of blood coagulation are well established: A coagulant (thrombin) is first formed from an inactive precursor (prothrombin) and then acts on fibrinogen to form fibrin. The formation of thrombin requires specific activators, notably ionized calcium and the phospholipid cephalin, and probably requires certain accessory factors. Antiprothrombins inhibit the conversion of prothrombin to thrombin. Antithrombins actually prevent the conversion of fibrinogen to fibrin by thrombin. The fundamental reactions are subject to a variety of nonspecific influences such as temperature, p_H, salt concentration, dilution and "wetting."

The plasma itself contains all of the necessary clotting factors, but obviously they are not all "available" in the circulating blood. Fibrinogen deficiencies are a cause of bleeding in certain hepatic diseases and allegedly in cases of pseudohemophilia. The defect is not in the clotting time but in the weakness of the clot formation (hence there is a prolonged bleeding time).

Prothrombin deficiencies accompany the hemorrhagic tendency in avitaminosis K of chicks, in certain toxic states (in animals), in hepatic and biliary disorders and in hemorrhagic disease of the newborn. Prothrombin is converted into thrombin via an intermediary colloidal compound containing definite proportions of prothrombin, calcium and cephalin. Clinical hypocalcemia is rarely (if ever) severe enough to have any significant effect on coagulation, and it is extremely doubtful

that the administration of calcium can be expected to exert any beneficial effect by assisting the clotting mechanisms. It is possible to prepare a prothrombin which is incapable of activation by calcium alone and requires some thromboplastic agent in addition. Cephalin (a phospholipid) is such an agent, but there are still other accessory factors. One, a trypsin-like "thromboplastic enzyme," perhaps acts by mobilizing the cephalin, which analyses show to be normally in firm, inert combination with the proteins present. Hemophilia appears to be caused by a deficiency of these new accessory thromboplastic factors in the plasma.

Clotting time is a linear function of thrombin concentration. If (and this is a moot point) all plasma prothrombin can be converted into a stable thrombin by the addition of calcium salts and thromboplastic materials, comparison of the valves for the clotting time of the patient's blood with normal values will indicate the relative prothrombin concentration. Besides establishing the correlation (see the foregoing paragraph) of certain hemorrhagic conditions with prothrombin deficiencies, the new methods of Quick and of Smith and his associates for determining the prothrombin level have made possible the rapid identification of the antihemorrhagic vitamin (K), which turns out to be a common factor to a number of 1, 4-naphthoquinones. Its clinical use should be confined to cases of prothrombin deficiency.

Bleeding in allergic states has been related to a loss of coagulability of the blood due to the outpouring of heparin from the liver. Heparin (a combination of mucoitin-polysulfuric acids with the base glucosamine) has two modes of action, namely, antiprothrombic (erroneously denied by some workers) and antithrombic (but only in conjunction with plasma albumin).

The analysis of the coagulation process thus affords a means for the differential diagnosis and possible treatment of a large group of hemorrhagic disorders. If, in addition, causative factors, including injury to the platelets and the capillaries, are given full consideration, the way is open for the solution of many of the problems of "the hemorrhagic diathesis."

DISCUSSION

DR. D. MURRAY COWIE, Ann Arbor, Mich.: I have followed the work of Dr. Ferguson and Mrs. Erickson closely and with great interest. In spite of all the extensive work that has been done, the true mechanism of blood coagulation still needs explanation. The subject, to say the least, is enticing when one gets to work on it. If I am not mistaken, the work that has been done by Mrs. Erickson in conjunction with Dr. Ferguson tends to show that under certain circumstances, in cases of hemophilia for example, the cephalin of the platelets and other tissue is bound and cannot be released, probably because of the quantitative deficiency of factors which resemble a trypsin-like ferment. I am glad to see the trend of thought again turning toward the idea I had so firmly fixed in my mind while working with Morowitz in Heidelberg in 1908. Thrombokinase, which, as the name indicates, was regarded as a ferment, was in the foreground at that time. The thromboplastins now spoken of are of the same nature; the use of the plural term indicates a step forward, that is, recognition that there is more than one ferment-like substance. What is now designated as prothrombin was called thrombogen in those days. I should like to hear from Mrs. Erickson, who will correct me if my interpretation is wrong.

MRS. BETTY NIMS ERICKSON: Investigations of the distribution of the phospholipids of the plasma in cases of hemorrhagic diseases have been made with a view to determining the amount present of the phospholipid cephalin which aids in clot formation. No lack in the total amount of plasma cephalin has been found in cases of hemophilia, hemolytic jaundice or thrombopenic purpura.

Since the addition of extremely minute amounts of pure cephalin is effective in promoting clotting, far less than the total quantity already present in the plasma and the platelets, it seemed imperative to investigate the amount of free cephalin present and the conditions under which it is made available. The data indicated that there is no free or unbound phospholipid, or only small amounts (less than 1 mg. per hundred cubic centimeters of plasma), in the blood. Thus, apparently all of

the phospholipid in the plasma is in complex combination with the proteins, and one might think of it as being unavailable for the purposes of blood coagulation. Do the platelets then function by release of free cephalin on their disintegration when blood is shed, as has been postulated in current theories?

The amounts of free and combined cephalin in extracts of lysed platelets were investigated; no phospholipid could be detected, which indicates that the platelets do not release their cephalin on disintegration. As Dr. Ferguson has shown, however, these extracts did contain a potent clot-promoting factor which was similar in action to trypsin, which accelerates clot formation, and to other tissue extracts containing the new coagulation factor, the proteolytic enzyme.

What relation the enzyme may have to the phospholipid factor and how the cephalin is mobilized from its inert combinations to the active prothrombin-calcium-cephalin complex must await further research.

Long Term Studies of Subnormal Growth in Children. Dr. Ernest H. Watson, Detroit.

The diagnosis, treatment and follow-up of patients suffering from disturbances in growth were discussed. The taking of the history is particularly important. Special inquiry should be made into the endocrine status of the mother and father, and the occurrence of goiter and allergic and constitutional diseases in the family should be recorded. The arm span, the length of the legs and the trunk and the circumference of the head, the chest and the abdomen should also be recorded.

When the height varies from the theoretic normal by more than 10 per cent, special investigation is indicated.

The leg length and the arm span, thought of as measurements of the long bones, are relatively reduced in cases of hypothyroidsm and relatively increased in certain pituitary disturbances, such as Fröhlich's syndrome, gigantism and hypogonadism. The arm span and the leg length are usually abnormally short in cases of hypergenitalism because of the early union of the epiphyses.

From birth until the tenth year the trunk makes up a considerable portion of the total body length. After this age the leg length predominates.

After the growth curve has stabilized, at about 2 years of age, yearly increments in height and weight are approximately 2 inches (5 cm.) and 5 pounds (2,268 Gm.) during the asexual phase. Preadolescence, which occurs at about the ninth year in girls and the tenth year in boys, is the signal for a marked "spurt" in growth. This shows up markedly in the individual record, but because it begins at different times in different persons it does not show up to the same degree in the composite, or average, growth curve. For proper record, measurements should be made at monthly or bimonthly intervals.

(Illustrative slides were shown.)

It is generally believed that endocrine disturbances in the parents may be reflected in similar or related disturbances in the offspring. A birth weight considerably below normal arouses the suspicion of hypopituitarism. Marked overweight at birth may be an evidence of hyperactivity of the pituitary or hypothyroidism in the mother and should lead to an investigation of the thyroid status of the infant. The child with hypothyroidism is markedly retarded with respect to sitting up, teething, talking and mental development, a situation which is not, as a rule, encountered in cases of hypopituitarism.

In older children marked statural overgrowth suggests hyperpituitarism. The concept of the Fröhlich syndrome needs to be qualified. The majority of children with this syndrome suffer from a deficiency of the gonad-stimulating hormone of the anterior lobe only. The tendency to be taller and larger than other children is evidence that the growth-promoting hormone is being produced in adequate amounts.

Unusual ease of fatigue and asthenia suggest adrenal insufficiency. Loss of weight, polyuria, polydipsia and digestive disturbances indicate hypofunction of

the digestive apparatus and may denote hypoactivity of the pancreas and liver or diabetes insipidus. Diabetes mellitus may cause a definite retardation of growth.

Factors influencing growth include heredity, prenatal care, environment, nutrition, endocrine function and disease. Nothing can be done about the first two. A great deal may be done to improve the environment and the nutrition and to decrease the incidence of disease (especially syphilis and tuberculosis). The presence or absence of disease should be determined as early as possible.

Chronic infections always exert untoward effects on growth and development. Tuberculosis, osteomyelitis and syphilis may seriously retard growth.

The practical application of the increased knowledge of nutrition is resulting in children who are taller and healthier than their parents. A thorough investigation of the nutritional state should be made regardless of the patient's economic status or other considerations.

In many cases it is the whole group of symptoms, rather than any single one, which enables one to arrive at a definite diagnosis. Unusual dryness of the skin, coarseness and sparseness of the hair, retardation of the physical, and more particularly of the mental, development and characteristic facies are important symptoms of hypothyroidism, while hypopituitarism causes general arrest of growth and development. Children with hypopituitarism are much too small for their age. The terms infantilism and nanism are frequently used to describe the pituitary dwarf. Hair of fine texture, smooth skin, symmetric features and attractive appearance are characteristic features. In many cases mental development is normal, or nearly so, in spite of retardation in physical development. Physical measurements are uniformly smaller than normal. Infantile body proportions and preponderance of the length of the trunk over that of the extremities, which are symptoms of hypopituitarism, are manifestations normally present in all infants at birth.

DISCUSSION

Dr. Arthur R. Turner, Chicago: I should like to ask Dr. Watson whether his studies included any routine roentgenograms of the wrists. I feel that a note of caution should be sounded in regard to the routine measurement of the circumference of the head. It is known that the greatest increase in the size of the head occurs during infancy, and certainly after the age of 5 years the annual increase in the size of the head is small. It is undoubtedly true that in Dr. Watson's practice, as in the hands of all workers who make anthropometric measurements, successive repetitions of the same measurement on the same patient at one examination will give varying results because of errors in technic. Statistical studies based on such measurements take these errors into consideration. The point to be made here in regard to the measurement of the circumference of the head is that the annual increase is small and that any measurement for which the annual increment is less than the probable error is of doubtful value.

Hematemesis: Observations on the Surgical Treatment of Esophageal Varices. Dr. L. Dell Henry, Ann Arbor, Mich.

Cases in which there is bleeding into the gastrointestinal tract without there being any lesions in the tract which are demonstrable roentgenologically have always been serious problems, encountered not infrequently by the pediatrician. The occurrence of a symptom complex consisting of hematemesis, splenomegaly, secondary anemia and sometimes cirrhosis of the liver has been reported on numerous occasions.

There is an extensive venous plexus at the gastroesophageal junction, which Kegaries has shown anastomoses with the portal system, including the splenic vein and the caval circulation.

Not until 1928 were esophageal varices demonstrated roentgenologically. Since that time numerous European and American workers have shown that such varices were present in cases in which there was bleeding into the gastrointestinal tract, usually in association with splenomegaly.

I had the privilege of following up 3 cases of esophageal bleeding, in all of which there was splenomegaly, while I was associated with Dr. Lester Dragstedt, at the University of Chicago Clinics. To date, Dr. Dragstedt has had 5 cases, in all of which there were bleeding into the gastrointestinal tract, splenomegaly and vomiting of blood on some occasions. In all 5 cases splenectomy was performed and the larger varices were ligated and into them injections of sodium morrhuate were made; for the smaller varices only injections were used. He had no unpleasant experiences with the operation itself. In 3 cases the injections seem to have obliterated the varices and prevented subsequent hemorrhage, while in 1 case the patient died, evidently from an esophageal hemorrhage six months after operation, and in 1 case the varices have apparently returned, as indicated by a checkup roentgen examination of the esophagus subsequent to operation. Dragstedt has expressed the belief that there is promise in this method of treatment.

I wish to report a case in which there were splenomegaly and esophageal bleeding. The patient, a boy now 12 years old, had his first severe hemorrhage at the age of 3 years and his second at the age of 5, when he made his first visit to the University Hospital. At this time his spleen was markedly enlarged. Splenectomy was performed after he had recovered sufficiently from the effects of the hemorrhage. Since that time, six and a half years ago, he has had four massive hemorrhages. Splenectomy alone has not cured this boy. His last severe hemorrhage was in September 1939. As soon as he has sufficiently recovered my associates and I plan to ligate and to make injections into the varices. We expected to do this several weeks ago.

There are numerous reports of cases of splenomegaly in which a diagnosis of esophageal varices was made, but only after bleeding into the gastrointestinal tract had occurred. None of the authors mentioned that esophageal varices were looked for before hemorrhage occurred. The first hemorrhage may be fatal; so avoiding it would be a good clinical procedure. I should like to urge that every patient with this syndrome be thoroughly examined. Some authors have expressed the belief that enlargement of the spleen which cannot be satisfactorily explained, even if there is no hemorrhage into the gastrointestinal tract, is sufficient indication for splenectomy and ligation of the coronary veins. Since the roentgenologist can now help to diagnose this condition, the surgeon can correct it in many cases before damage is done.

DISCUSSION

DR. FRED J. HODGES, Ann Arbor, Mich.: The recognition of esophageal varices during fluoroscopic examination of the upper part of the gastrointestinal tract is as a rule not difficult. It is necessary, however, that the examiner be on the alert and that he observe the esophagus under varying conditions if the characteristic pattern of enlarged and tortuous vessels is to be seen.

Search for varicose veins beneath the esophageal mucosa is best carried out with the patient supine and rotated toward the right, under which circumstances the esophagus will be found between the thoracic portion of the spine and the shadow of the heart, clearly outlined against the transparent lung. It is best to use barium sulfate or a salt of some other heavy metal suspended in a medium of high viscosity which will permit the opaque material to cling to the mucosal surface. Placing the patient in a horizontal position retards the speed of esophageal emptying. Although it is impossible to manipulate the esophagus from without, the patient by closing the glottis and attempting to exhale forcibly can bring about an increase in intrathoracic pressure which will reduce the rate of venous return to the auricles. Under these circumstances venous engorgement occurs, and if there are enlarged, tortuous submucosal vessels in the esophagus a characteristic imprint is produced on the opaque material. This type of examination must, of course, be greatly modified if one wishes to study the esophagus of an infant, for intelligent cooperation is required if this method is to be used. The demonstration of tortuous, engorged veins along the course of the esophagus is a reliable sign. However, failure to demonstrate their presence does not preclude the existence of esophageal varices.

Two Cases of Unusual Malformation of the Colon. Dr. Mark Osterlin, Traverse City, Mich.

A report of 2 cases of congenital microcolon in a newborn infant in which there were failure to pass meconium and early vomiting, with abdominal distention, was presented, with the findings at autopsy.

DISCUSSION

Dr. Smith, Detroit: Treatment in such cases is surgical. Though the patient is usually a poor risk, there is a possibility of the operation's being successful, but early diagnosis is essential.

Dr. B. W. Carey, Detroit: Ileostomy should be done first.

Dr. Mark Osterlin: Ileostomy was performed in each of these cases, but no benefit resulted. Another evidence of obstruction is early distention.

Nutrition of Children and Adults. Dr. George M. Brown, Bay City, Mich.

The purpose of this paper is to correlate some of the observations on adults, both in health and in disease, with the habits of nutrition formed early in life. Pediatricians, of course, have a full understanding of the importance of the proper nourishment of infants and young children. There has been little emphasis given to the importance of continued attention to the factors necessary to maintain the health of a person at the highest possible level from the time he begins to choose his own diet through the entire growing period and young adult life. One seldom finds a layman who has any concept of what constitutes a balanced diet for a human being. I feel sure that this ignorance is partly due to the lack of instruction given by the average physician. The majority of physicians have no definite concept themselves of what constitutes a normal balanced diet, and few have any brief method of explaining it to their patients so that a clear understanding is reached. A thorough education of physicians and of the lay public is needed.

These conclusions have been reached:

1. The first and chief reason for dental caries is insufficient nourishment before birth because of a deficiency of calcium and vitamin D in the mother's diet.

2. The second reason for dental caries in children is a deficiency in the amount of vitamin D ingested during the entire growing period.

3. The real cause of pyorrhea is the lack of sufficient amounts of vitamins B and C in the diet. Infection would never start in the gingival margins if the gums were properly nourished at all times.

4. A child who is blessed with a good set of teeth in the beginning and who eats a diet that is properly balanced all his life will never need artificial teeth.

5. A person with a healthy set of teeth is usually healthy in every other way.

6. There is a lack of precise teaching, both of physicians and of the public, of the necessity for consuming a balanced diet at all times.

7. If sufficient attention were given to this subject and if properly balanced diets were consumed by the entire public during the full length of life, I believe that most of the painful chronic conditions of adults would be prevented.

8. To be healthy and comfortable during the last forty years of life one must eat correctly during the first forty years.

Structural and Psychologic Changes After Cerebral Accidents in Children. Dr. Bronson Crothers, Boston.

In this discussion the effect of disease or injury of the brain on the growth and development of the child is considered. There are certain striking differences between children and adults which need periodic and emphatic restatement.

First, the child is not self maintaining in any effective way. Economically his security is that of his parents. Emotionally he is more or less blindly fighting

against authority or suddenly craving protection. Intellectually and physically he is steadily progressing toward effective, competitive adult life.

Second, if he becomes ill he loses effectiveness, as do adults, but his recovery needs to be defined in special terms. The young adult may be reduced to complete mental and physical helplessness. As soon as he regains the capacity to carry out the business of living with effectiveness and satisfaction, he and his physician speak confidently of recovery. He is as well as ever. The elderly person is satisfied if he is able to do almost as much as ever. All he asks is that the orderly deterioration, which he accepts, should not be accelerated.

When a child has been seriously ill for a prolonged period, it is no longer possible to accept restitution to a previous state as unequivocal evidence of recovery. It must be demonstrated that orderly growth and development are established. Every one who deals with children accepts this idea readily enough, but few make any particular effort to establish standards of growth, particularly in the mental and emotional fields.

At the Children's Hospital in Boston children with neurologic disorders have been treated under the critical eye of Dr. Elizabeth Lord, a psychologist of wide experience, who views medicine and its practitioners with skepticism. As a result my associates and I have been forced to put our ideas about cerebral lesions into proper form.

In general it is recognized that the medical mind deals well with deficits. Anatomic or physiologic deficits lead directly to classification and to medical or surgical intervention. On the whole, physicians regard the study of deficits as indispensable, and they are correct in so thinking. However, psychologists, and still more, teachers, are eager to identify assets. What has happened is that physicians have had to try to organize their ideas so that the medical deficit suggests the educational assets. The method can be illustrated by various cases. A child becomes ill. He loses consciousness, he has weakness of one side and perhaps he has convulsions. The physicians identify the deficit by using all the proper diagnostic methods, including such measures as encephalographic and electroencephalographic examinations. The surgeon may or may not intervene. Then improvement begins, and every one tries to identify the various points which make prognosis possible.

The state of the child before the accident is reviewed with great care, so that a clear picture of development is recorded. Psychologic appraisals at intervals indicate first a restoration to the previous level and then an ability to progress beyond that level. Finally, in favorable cases, evidence of restitution of a normal rate of growth and of emotional stability can be shown.

The evidence that has been collected suggests that after severe and prolonged disability resulting from injuries or infections recovery is often in doubt over a period of years. Great care and conservatism are obligatory before "arrest of development" is accepted as a permanent state. On the other hand, it is equally essential not to decide to use "recovery" as a basis for management before all the evidence is in.

(Slides and moving pictures illustrating various types of cerebral damage were shown.)

DISCUSSION

DR. M. M. PEET, Ann Arbor, Mich.: There is no surgical procedure which can be used for the type of patient discussed tonight by Dr. Crothers. It is self evident that if the brain is seriously damaged surgical procedures are not going to restore it.

However, the effects of a few types of birth injuries can be lessened if the child is treated early enough. When one speaks of birth injuries, one usually thinks of intracranial hemorrhage. The original mortality is high, but many babies survive the initial injury. If the presence of gross hemorrhage can be recognized, operation is indicated. Hemorrhage in the subarachnoid space apparently interferes with the outflow of waste products from the cortex or in some other way causes an injury which later results in cortical atrophy. Lumbar punc-

ture once or twice a day until all the accumulated fluid blood has disappeared may do much to prevent subsequent trouble. Of course, there are many birth injuries which are not due to hemorrhage. These are not necessarily injuries in the sense of being gross lesions, but they can certainly do as much toward producing spasticity or feeblemindedness in the child as can hemorrhage. The effect of lesions of this type cannot be lessened by any operation carried out on the cranium or within it.

The lesion most amenable to surgical intervention is the rather common chronic subdural hematoma. The presence of an intracranial lesion is usually not suspected until the baby is 3 or 4 months old, although there may have been feeding problems from the beginning which numerous changes in the formula did not solve. Frequently the most noticeable thing about these children is the large head, which suggests hydrocephalus. I have been impressed, however, with the fact that children with subdural hematomas look much brighter than do those with hydrocephalus, who generally appear rather apathetic. The differential diagnosis of these two conditions is exceedingly important, because nothing can be done for the child with true hydrocephalus, while the child with a subdural hematoma can be saved, if the condition is recognized early enough. How extensive should be the examination by which one attempts to differentiate these two conditions? Is bilateral puncture of the fontanels sufficient? In some cases I have been satisfied with this procedure, but some hematomas are in the posterolateral position and I have even seen some beneath the tentorium. To be certain not to overlook a hematoma when its presence is suspected, a small opening, with the use of local anesthesia, should be made in the posterior parietal region or an encephalogram should be made.

At times one can tell on which side the lesion is located by percussion, since there may be an entirely different note on that side. Percussion also may aid in differential diagnosis, because when hydrocephalus is present a higher tympanitic note is elicited than when the lesion is a subdural hematoma.

In my experience the operative procedure carried out on children must differ from the operation for the same condition on adults, because the baby's brain is too soft to expand under the compression of the thin, but tough, inner membrane. Therefore, a small flap of bone is turned back and the contents of the hematoma everted. The inner membrane is then picked up and cut in a stellate manner, so as to allow the brain to expand and fill in the defect left by taking out the hematoma. Placing the child in a head-down position will also help.

DR. T. RAPHAEL, Ann Arbor, Mich.: I have been much impressed by Dr. Crothers' emphasis on the fact that in treating damaged children one is dealing with growing and unfinished organisms. This point is of vital importance and is an absolute *sine qua non* with reference to the establishment of any really constructive procedure or process in therapy. I feel this aspect has not been given by any means as much recognition as it deserves and that it cannot be stressed too strongly. It occurs to me also to emphasize at this time the desirability of a proper understanding and appreciation of the constitutional or basic personality pattern of the type of children discussed. It certainly is important to be sure that the therapeutic approach to children as handicapped as these is formulated in terms of the qualities and possibilities which the child possesses, as well as in terms of the resources and potentialities which he does not possess. It also occurs to me to stress a practical point, that is, the great need for more facilities, institutional and extrainstitutional, for the proper treatment and management of the types of patients here considered. For these patients, handicapped as they are, treatment and direction must often be prolonged and sometimes must be lifelong. If facilities for such treatment, including trained personnel as well as physical facilities, are not available, it is obvious that much that had been accomplished may be nullified. There is really a great need for the expansion of facilities of both the intracommunity and the institutional type. In this plea, I am sure, Dr. Crothers will bear me out.

DR. FREDERIC SCHREIBER, Detroit: The pediatrician must be impressed with the wariness and hedging with which the neurosurgeon approaches the diagnosis, and especially the prognosis, of lesions of the brain in children of the type which Dr. Crothers has discussed. By watching such children grow up one finds that they respond differently to insults to the brain than adults do. It is as if one were observing an early episode in a moving picture film, the development of the story and the later sequences being hidden from the observer. Inadequate histories, the resilience of the infant skull, the late effects of gliosis and the compensatory adaptations peculiar to the child make predictions uncertain.

Although the localized damage to the brain may be striking in children who have suffered trauma or who have subdural hematomas, the generalized deterioration in children who have been subjected to severe cerebral asphyxia is much more subtle and devastating. In the brains of children with unilateral subdural hematomas shown by Dr. Crothers, the clinical and encephalographic changes were fairly well restricted to one hemisphere. However, in the brain of the child who survived asphyxia by fire and in that of the one who showed evidence of cerebral anoxia when ether was administered for the removal of a gangrenous appendix, the cerebral disintegration was generalized and progressive. That is why the recognition of the controllable anoxic factors associated with the analgesia and anesthesia of the mother during delivery is so important. The ultimate effects on a child of devastating cerebral anoxia are the same, whether they are due to asphyxia from fire or to the administration of drugs to the mother during delivery. Those physicians who have occasion to examine such children and have to talk to their distraught parents cannot emphasize too strongly the value of any study aimed at the prevention of asphyxia at birth. It makes one sick at heart to see such damaged children later and to realize that nothing can be done about their fixed lesions.

The results of surgical treatment are gratifying in children with subdural hematomas for whom the diagnosis has been made early. When, however, the brain has been squeezed far over and a thick membrane of fibrin has been laid down, the results are often discouraging, and it is therefore wiser when in doubt to explore the subdural space early. A condition which sometimes simulates subdural hematoma in infants is a subdural collection of clear fluid, probably as a result of a small tear in the arachnoid. Allowing this fluid to be absorbed under the scalp after trepanning clears up the neurologic symptoms, which usually consist of lethargy, spasticity or convulsions.

DR. ALFRED A. STRAUSS, Northville, Mich.: The neurologist who deals with children is well aware of the differences between the practice of neurology among children and that among adults. But what is greatly needed is a discussion of the evaluation of neurologic signs and symptoms in the child. For example, the Babinski sign is considered as a symptom referable to the pyramidal tract. It is present in the newborn infant and disappears at about the age of 2 years. It is important to question whether or not this physiologic Babinski sign is of the same origin as the pathologic Babinski sign in adults. I doubt it, and I think that many investigators have shown clearly that the origin of the Babinski sign of the newborn infant is in the extrapyramidal system. If this assumption is correct, the further question of the diagnostic value of the Babinski sign is to be raised: How long does the physiologic Babinski sign persist? What type of Babinski sign appears in children after the age of 2 years? Is the Babinski sign which is present after the age of 2 a symptom of motor retardation or of a defect in the motor system? I have collected some material relevant to this problem, but discussion of it would lead me too far afield.

I wish to point to certain observations which have a bearing on the time factor in neurologic conditions in children, a concept stressed by Dr. Crothers. I found that among children whose mental defect was organic in origin the typical dull facial expression was not present in those who suffered damage to the brain after the age of 1 or 2 years. This fact can be interpreted to mean that mimetic movement has reached a stage by the age of 1 or 2 years of specific activity and is

independent of general motor behavior. Another example: The Oppenheim, Mendel-Bechterew and Gordon signs, which indicate a lesion of the pyramidal tract, are rarely found in children with birth injuries but are more frequently found in children whose brains have been damaged in later years.

My own investigations lead me to concur in Dr. Crothers' view that the time factor is an important element which should be considered in all future investigations concerning diagnosis, pathogenesis and prognosis of neurologic disturbances in childhood. Three kinds of time factors should be differentiated: (1) time with respect to ontogenesis (Monakow's chronogeneous localization)—the phase of maturation, separated into germinal, prenatal, natal and postnatal periods; (2) time with respect to restitution—the duration of complete or partial restitution, and (3) time with respect to the pathologic process—whether the destruction takes place only once or many times over a short or long period.

Dr. Carl Badgley, Ann Arbor, Mich.: I am glad that so much interest in this problem has been displayed here, because it is one that must be faced. It has been my experience that one third of the patients at many of the clinics for crippled children throughout the state belong in this group. Many of them are hopeless, vegetative animals. For the remainder, so far as I can see, the only physicians interested in their care have been the orthopedic surgeons. Physicians have failed to handle the problem. They have not assumed the responsibility which is theirs. One of the outstanding reasons for this is that all physicians want to be successful in handling the patients they take care of. It has been my observation that frequently Dr. Peet cannot do things that I can do, and I am glad that he has acknowledged it, because surgeons can operate and markedly improve some of these children. Dr. Peet was speaking entirely on the basis of injury to the brain itself. Many suitably selected patients with spasticity are markedly improved by neurectomy. There is little difficulty in obtaining satisfactory function in the leg for weight bearing, but when it comes to the complicated functions of the upper extremity, there is a great deal more trouble. Given a patient with a certain level of intelligence, one can do much for the upper extremity. I have just seen 2 patients who had involvement of the arm for whom transplantation of tendons and arthrodesis of the wrist secured excellent functional results.

One speaks of physical therapy as a means to an end, but there are few physicians who are qualified to instruct physical therapeutists in the technic of coordinated exercises.

I think the conclusion reached by this group should be that it is the responsibility of the members of the medical profession to face the facts, to see what can be done collectively for such patients and not to attempt to shift the load. Aiding such patients is not the function of any single medical specialist. It will require a combination of all that medicine has to offer to handle this problem. It is a problem which the Crippled Children Division of the Children's Bureau, U. S. Department of Labor, is now beginning to recognize and consider.

Dr. Bronson Crothers: I don't know that it is possible in the remaining time to answer the questions that have been brought up or to go over the wide field that has been covered. There are one or two things which I feel it is essential to point out. In the first place, Dr. Peet did not do himself justice in suggesting that he looked for hemorrhage in children with big heads and bright eyes. He knows as well as I do that big hematomas can occur in children without increased intracranial pressure.

Another question that comes up is whether all physicians should be doing subdural punctures. I don't believe so, for such punctures may have to be followed almost immediately by further surgical operations to stop the oozing which may start. I myself should like to limit the performance of subdural punctures to physicians in hospitals, where immediate neurosurgical procedures can be carried out if they are needed.

It seems clear to me that physicians have not really faced the ultimate problems that arise as a result of cerebral injuries in children. Most physicians can handle these children if they have some simple machinery and some optimism, but I believe

that any one who has seen older patients with cerebral palsy has realized the high incidence of complete frustration among such patients; and the fault lies to a large extent in the optimistic, rather dodging, attitude of the physician, who has assumed that if the child has a relatively intact intellect he can be educated to any desired extent. Some of these children, for instance, are being trained as creative writers, and absurd vocational suggestions of this sort may be expected until the fact is faced that 90 per cent of the children who have cerebral injury need not cheering up but a searching attempt to find a solution that is reasonably adequate for them. The present educational system breaks down all the time in this respect. Any approach which does not include a definition of possible educational objectives is obviously incomplete.

Management of Changes in Personality Occasioned by Cerebral Accidents in Children. Dr. Paul H. Jordan, Ann Arbor, Mich.

It is assumed that by the term cerebral accident is meant not only physical trauma to the brain occurring at birth or at a later period but injury to the brain resulting either directly or indirectly from some agent, whether mechanical, vascular, infectious or chemical. It must be remembered that the child is a feeling, experiencing, growing organism which reacts constantly to stimuli from the external environment and from within itself. Anything which affects one part of this growing organism is likely to affect its total functioning.

Changes in personality may result either directly or indirectly from injury to the brain. Direct changes are dependent largely on the area of the central nervous system involved and on the extent of the damage to nerve tissue. Injury to the brain may result directly in varying degrees of decrease in the capacity for intellectual functioning. The general intelligence may be reasonably intact although certain intellectual processes, such as retentive memory and associative thinking, are impaired. Involvement of the peripheral or central nervous system may result in interference with visual or auditory sensory perception and association or in impairment of oculomotor functioning, serious obstacles to the child in mastering such academic skills as reading. Cerebral injuries frequently result directly in various types of alteration of motor control, which limit the child in his capacity for adjustment to his environment and interfere with his intellectual and educational growth through experience. Important changes in behavior may result directly from injury to the brain, that is, from damage to the basal ganglions. These changes involve primarily a development of emotional lability or instability and a reduction in the ability to control the more aggressive impulses. It is difficult to decide how much of these severe disturbances in behavior is the direct result of pathologic changes in the brain and how much is the reaction to various stresses prematurely placed.

An injury to the brain may indirectly affect the personality in many ways. Anxiety over the child, reflected in overprotection and overindulgence, may handicap him further in his adjustment by depriving him of the opportunity to grow through experience and by establishing a pattern of excessive dependence. At times parents stimulate the child beyond his capacity to respond, thereby producing inhibition of development rather than an acceleration. Parents are often unable to accept the permanency of the child's handicap, and they unconsciously react toward him in a hostile manner and deprive him of necessary security, affection and understanding. Because of an injury to the brain the child's personality may be indirectly adversely affected through lack of educational experience and failure to adjust the educational program to meet his limitations and needs. The reaction of the child to his handicap has an important influence on the personality pattern which subsequently develops. If he finds himself continually frustrated in his desire to achieve success, recognition and equality with those about him, he may become discouraged and disheartened and may manifest a tendency to rebel and express his resentment in aggressive behavior.

The management of cerebral injury begins with a careful evaluation of the intellectual functioning, the extent of the damage to the brain, the nature and extent of the physical handicap, the attitudes of the parents and others toward his disability and the resources available for utilization in the program of treatment. This needed information can be gained through careful psychologic study, neurologic examinations, observation and interpretation of behavior and by obtaining an adequate social history. While the program of treatment may be instituted after one such evaluation, all aspects of the case should be carefully reevaluated at fairly frequent intervals.

The program of treatment should be adapted to the limitations and needs of the patient, the primary objectives being to relieve him of needless stresses and to provide adequate opportunity for optimum physical, intellectual, emotional, educational and social growth. Some patients are totally incapable of adjusting satisfactorily in the community or are unable to find there the type of care they require. Those who are educable should be treated in a specially designed psychiatric hospital for children; those who remain seriously retarded mentally profit most by permanent placement in a custodial institution.

Some children will require a minimum of orthopedic treatment and physical therapy. A certain percentage will profit by surgical procedures, physical therapy, occupational therapy, psychotherapy and educational measures. Unfortunately, the facilities provided are inadequate to meet the needs of many of these children.

Treatment of Experimental Eastern Type Equine Encephalomyelitis and Its Possible Bearing on the Treatment of Encephalitis in Children.
Dr. J. E. Kempf, Ann Arbor, Mich.

Equine encephalomyelitis has probably been present in this country for the past century, but the first scientific knowledge of this disease was not obtained until 1930. It was first described in horses in California as western type equine encephalomyelitis. In 1933 a more virulent form appeared along the Atlantic seaboard. This form of the disease was serologically different from the western variety and was designated as eastern type equine encephalomyelitis. The first of many cases in which an accurate diagnosis was made occurred in Massachusetts in the summer of 1938.

The epidemiologic characteristics of the disease are uncertain. Ticks and a number of varieties of mosquitoes which have been infected in the laboratory have infected laboratory animals, but these insects have not as yet been found to harbor the virus naturally. The virus has been isolated from wild gophers, pheasants and pigeons. In man the disease attacks males as frequently as females; it shows a predilection for children, 69 per cent of the persons infected being under 10 years of age.

The onset in younger children is usually sudden, with a rise in temperature to 104 F., drowsiness or irritability, cyanosis and convulsions. In older children the onset is slower and is accompanied by frontal headaches and dizziness. Diarrhea, vomiting, muscular twitching, tremor, rigidity of the neck, a positive Kernig sign, hemiplegia and paralysis of the face may occur. Most patients are semicomatose or comatose on admission to the hospital. On the average, the spinal fluid is under a pressure of 240 mm. of mercury and contains 200 to 2,000 polymorphonuclear leukocytes, and its protein content is 185 mg. per hundred cubic centimeters. The mortality rate is about 66 per cent. Sequelae are severe.

There is no standard method of laboratory diagnosis. Usually the titer of antibodies against the equine encephalomyelitis virus is determined by neutralization tests, in which graded dilutions of a known suspension of virus mixed with the patient's serum are injected intraperitoneally into young mice and the results compared with those from injecting mixtures containing normal serum. Microscopic examination of tissues and isolation of the virus after death are other methods. In the epizootic areas the disease takes an unusually severe form and consequently it may be diagnosed at an early stage. In its milder form it is almost impossible to diagnose

It has been found that persons who come in contact with the virus have antibodies in their blood, while those who have not had such contact do not. Neutralizing antibodies were present in the blood of 23 of 69 laboratory workers who had not had symptoms of the disease. Seven days after vaccination there is a titer of antibodies in the blood sufficient to protect mice against a large number of minimum lethal doses of the virus suspension. Vaccination of all persons in the region of an epidemic among horses should be considered to avoid the high fatality rate and the tragic sequelae of the disease. Serum therapy may be of value early in the disease. Its ineffectiveness if the disease is well advanced has been established. However, in a person known to have been infected in the laboratory the disease developed, and the patient rapidly went into coma. He was treated with 1,400 cc. of antiserum in divided doses and made an uneventful recovery. Hypotonic, isotonic and hypertonic solutions of sodium chloride have been used to no avail in the treatment of animals experimentally infected. Sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) have no effect on the course of the disease. Urea, given to stimulate the autolysis of dead tissue and to increase the defense of tissue against local infection, is of no value.

Equine encephalomyelitis is a potential public health problem, with special reference to the younger age groups. Vaccination of persons in epizootic areas should be considered. Antiserum may be of value in the early and in the advanced stages. Specific measures are of no value in treating the experimental animals.

Studies on Water and Electrolyte Balance of Patients with Bronchial Asthma. Dr. John M. Sheldon, Ann Arbor, Mich.

Five patients in whom attacks of bronchial asthma could be initiated and terminated as desired were studied with regard to their metabolism of water, sodium and potassium. In 3 patients asthmatic attacks were initiated by foods and in 2 by inhalant allergens.

The asthmatic attacks were associated with a considerable loss of body water, a distinct elevation in urinary sodium and a reduction of urinary potassium. The sodium depletion was directly related to the loss of body water. In the period of recovery from an attack, the urinary sodium was less than the amount of sodium ingested, but within a few days sodium excretion again returned to the level present before the attack. The loss of body fluid occurred in spite of distinct edema of the shock organ. It follows that a redistribution of fluid and electrolytes involving all tissues takes place and that in this redistribution there is a loss of water through the kidneys and an increase in the fluid content of the shock organ tissue.

DISCUSSION

Dr. D. Murray Cowie, Ann Arbor, Mich.: I have been interested in the edema or water retention in hay fever and asthma for a long time and am much interested in this splendid piece of work which Dr. Sheldon has done. The methods of cure or amelioration, those that make the patient better by reducing the swelling of the mucous membranes, are necessarily dehydrating processes. On request, when pitressin first came on the market, Parke, Davis & Co. furnished me with a large supply. I wanted to see what would happen if I gave it to patients with hay fever and asthma. A large percentage of them were made worse. This was just another point in favor of the idea of water retention. I have hoped all these years that some chemical method would be developed that would make it unnecessary to carry out the long desensitizing process. All physicians have used calcium chloride a great deal and have secured relief for many patients, but it was not enough. Recently, improved methods of antigen desensitization have been more successful. I hope that Dr. Sheldon will discover a pleasant way to eliminate sodium, which, perhaps, can be assisted by such dietary measures as the bread-free diet used in Ménière's disease.

Effect of Various Preservatives on the Maintenance of Sterility of Allergic Extracts. DR. JOHN J. ENGELFRIED, Ann Arbor, Mich.

The following chemicals have been studied: phenol, the methyl ester of parahydroxybenzoic acid, merthiolate, ethyl alcohol and glycerin. The methyl ester of parahydroxybenzoic acid has been used in this laboratory for the past five years, with satisfactory results. This chemical, originally sold under the German trade name "nipagin," is now referred to as tegosept M. A 0.20 per cent concentration in an isotonic solution of sodium chloride will prevent the growth of most organisms. However, it is not satisfactory as a bactericidal or bacteriostatic agent for Bacillus subtilis. The propyl ester (nipasol, or tegosept P) and the benzyl ester (tegosept B) of this acid are not suitable for us because of their low solubility in solutions of sodium chloride. The solubility of the methyl ester is approximately 0.25 to 0.30 per cent (varying with different lots of the compound), while the solubility of the propyl and benzyl esters is less than 0.05 per cent.

In this investigation the preservatives were dissolved or diluted in sterile broth. Nine cubic centimeters of broth contained such a quantity of the preservative that when 1 cc. of a broth culture of the organism was added the resulting concentration of the preservative was that percentage indicated in the table.

Each of the four organisms used (Staphylococcus aureus, Bacillus typhosus, Bacillus coli and B. subtilis) was subcultured in broth for four successive days. The fourth twenty-four hour culture was used to inoculate the various tubes containing different percentages of the compounds previously described. Two loopfuls of the contents of each of these inoculated tubes was transferred to broth (containing no preservative) after one, four, seven and twenty-eight days' exposure to the described chemicals.

The results obtained (table) show that a 0.4 per cent concentration of phenol was effective in killing three types of organisms within twenty-four hours but was not capable of killing B. subtilis within twenty-eight days. The methyl ester of parahydroxybenzoic acid (0.2 per cent concentration) was bactericidal for the same three organisms in seven days.

Phenol (0.30 per cent concentration), the methyl ester of parahydroxybenzoic acid (0.20 per cent), ethyl alcohol (14 per cent) and glycerin (25 per cent) are bactericidal for Staph. aureus, B. typhosus and B. coli within twenty-eight days. However, these preservatives (in the concentrations given) are not bactericidal or bacteriostatic for B. subtilis.

Merthiolate (0.005 per cent concentration) is bactericidal for all four organisms within twenty-four hours.

Types of Pneumococci in Children with Pneumonia and in Those Without Infection of the Upper Respiratory Tract. MR. ROBERT B. LINDBERG, Ann Arbor, Mich.

It is being increasingly realized that the many types of pneumococci discovered since types I, II and III were recognized are of especial importance in the pneumonias of children. Bullowa and Greenbaum, Andrews, Nemir, Raia and Cooley and Carey, among others, have presented information as to the incidence of various types of pneumococci in children. Differences between the flora of infants up to 2 years of age and of children up to 12 years of age have been noted; type XIV is especially prevalent in infants, and type XIX appears frequently in older children.

The study being reported on was an attempt to evaluate the throat swab technic, as originally described by Vinograd, Nemir and Park in 1936, for obtaining material for pneumococcus typing from infants and children. Material obtained by swabbing deep in the throat was placed immediately in broth and the broth centrifuged. The sediment was examined directly, it was cultured and it was injected into mice. Typing was carried out on that material which was most suitable in each case.

The technic was followed with 44 patients with pneumonia between December 1938 and March 1939 and with 76 children and infants without evidence of infec-

Effect of Preservatives on Growth of Organisms in Broth *

Organism		Staph. Aureus				B. Typhosus				B. Coli				B. Subtilis			
Time of exposure to preservative, days		1	4	7	28	1	4	7	28	1	4	7	28	1	4	7	28
Phenol, percentage concentration	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
	0.4 †	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
	0.3	+	0	0	0	+	0	0	0	1	0	0	0	0	+	+	+
Methyl ester of parahydroxybenzoic acid (tegosept M), percentage concentration	0.30	0	0	0	0	+	0	0	0	0	0	0	0	0	+	+	+
	0.25	0	0	0	0	+	+	0	0	0	0	0	0	0	+	+	+
	0.20 †	+	0	0	0	+	+	0	0	+	0	0	0	0	+	+	+
	0.10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Merthiolate (aqueous solution), percentage concentration	0.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.01 †	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.005	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ethyl alcohol, percentage concentration	20.0	0	0	0	0	+	+	0	0	0	0	0	0	+	+	+	+
	14.0 †	0	0	0	0	+	+	+	0	+	+	0	0	+	+	+	+
Glycerin, percentage concentration	50.0 †	+	0	0	0	+	+	0	0	+	0	0	0	+	+	+	+
	25.0	+	+	0	0	+	+	+	0	+	+	0	0	+	+	+	+
Sterile broth control	....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

* The symbol 0 signifies that there was not and + signifies that there was growth in twenty-eight days.
† The percentage of this chemical generally used for preserving allergic extracts.

tion of the upper respiratory tract in the outpatient clinic and the pediatric wards of a hospital.

For 34, or 44.6 per cent, of the normal children, cultures were positive for pneumococci, as follows: type XIX, 5 (14.7 per cent); type VI, 4 (11.8 per cent); types XIV, IX, VIII and II, 3 each (8.8 per cent); types I, IV, X and XI 2 each (5.9 per cent); types III, VII, XXII and XXIX, 1 each (2.9 per cent), and untypable pneumococcus, 1 (2.9 per cent).

The cultures for 36, or 80 per cent, of the patients with pneumonia, yielded pneumococci, as follows: type I, 14 (38.8 per cent); types III, IV, V, VI and XIV, 3 each (8.3 per cent); types II, VIII, XII, XVI, XIX and XXIX, 1 each (2.8 per cent), and untypable pneumococcus, 1 (2.8 per cent).

In 16 cases in which a preliminary diagnosis of pneumonia was made but subsequently disproved, specimens were taken and treated in the manner described. No pneumococci were found in any of these cases.

Of the remaining 8 cases in 4 the infection was probably caused by beta hemolytic streptococci, in 1 by alpha streptococci and in 1 by gamma streptococci, judging by the cultures of material from the throat and the pleural fluid in each case. Pleural effusion developed in 4 cases of pneumococcic pneumonia, and in each case the organism recovered from the pleural fluid was of the same type as that found in the material from the throat.

In 2 cases two types of pneumococci were recovered. In 4 cases culture of material from the first swabs was negative for pneumococci, but cultures of material from the second swabs were positive for these organisms.

Exclusive of those cases in which it is strongly indicated that the pneumococcus was not the infecting agent, in 95 per cent of the cases of pneumonia pneumococci were recovered by use of throat swab technic. It appears that in cases of pneumococcic pneumonia the technic gives accurate results in a high percentage of cases, but the possibility of recovering the organism in cases in which the pneumonia is not of this type must be borne in mind. Despite the necessity for caution in interpretation, the results indicate that prompt typing of the organism in cases of pneumonia in infants and children can be carried out with the throat swab technic with sufficient accuracy to be of value.

DISCUSSION

DR. ARTHUR R. TURNER, Chicago: It gives me a great deal of pleasure to hear a paper of this sort, because it indicates that in spite of the newer forms of therapy, which have been found so effective, there is still being manifested a scientific interest in the types of pneumococci with which one must deal. I recently heard a paper in Cincinnati on pneumonia therapy in which it was stated that because sulfapyridine has such a remarkable curative effect on all types of pneumonia it is unnecessary to determine what type of pneumococcus is present. This attitude seems to me unscientific and unwholesome, and I am glad that Mr. Lindberg's paper indicates continued interest in what I like to think is the scientific attitude.

Production of Immunity by the Intradermal Injection of Diphtheria Toxoid. DR. ARTHUR P. KELLER, Ann Arbor, Mich.

I have attempted to compare the subcutaneous and intradermal methods of administering diphtheria toxoid with regard to the frequency of reactions and the production of immunity, as determined by the Schick test.

In 1916 Dr. Cowie showed that small doses of toxin had an immunizing action, which was evidenced by a lessening of the severity of the local reaction (reduction in the area of erythema and swelling) to repeated small doses of toxin. Likewise, Bauer in 1918 proved that toxin in small doses had an immunizing action. Glenny and Allen, working with man and with rabbits, showed that the Schick test acts as a stimulus to the production of immune antibodies to diphtheria. It is also known that repeated Schick tests will raise the antitoxin titer of the blood serum

to a protective level. Goldbloom and Klein, in Montreal, Canada, used concentrated toxoid, administered intradermally, for persons who had positive reactions to the Schick test. Kern and his associates have claimed that the intradermal method of administration is as effective as the subcutaneous injection of a single dose.

To a group of 80 employees, nurses and students of the University Hospital, two doses of 0.1 cc. of toxoid were given intradermally, one week apart. To another group of 104 persons a total of 2.5 cc. of the toxoid in four doses was given subcutaneously at weekly intervals, as follows: 0.25, 0.50, 0.75 and 1 cc. At the end of four to six months Schick tests were performed. If the reaction to the test was negative, the subject was discharged; if positive, the toxoid was then given intradermally, and after a similar period had elapsed another Schick test was done. Results are given in table 1.

TABLE 1.—*Results of Schick Tests Performed Four to Six Months After Injection of Diphtheria Toxoid*

Method	Number of Subjects	Total Dose, Cc.	Interval Between First and Last Injection, Wk.	Reaction to Schick Test		
				Negative	Positive	Pseudo-positive
Intradermal	33	0.2	1	29	4	1
Subcutaneous	69	2.5	3	57	6	6

There were numerous slight reactions, so classified because only local redness and swelling occurred at the site of injection. The percentages of reactions among the subjects receiving the toxoid intradermally (58.7) and subcutaneously (52.8) were similar.

TABLE 2.—*Reactions to Injection of Unmodified Diphtheria Toxoid*

Method	Number of Subjects	Type of Reaction		
		Slight	Mild	Severe
Intradermal	80	47	22	11
Subcutaneous	104	55	26	23

In each group there were severe reactions when the Schick test was repeated. They were general and immediate, characterized by marked swelling and redness at the site of injection of the toxin and the control material, urticaria, pruritus, edema of the face and, in some, edema of the lips and pharynx. Of the group given toxoid intradermally, all who had reactions to the second Schick test had received previous subcutaneous injections of toxoid. One subject had a marked general reaction to the second Schick test. Among the subjects given subcutaneous injections of toxoid, only 2 reactions to the second Schick test were noted.

Intradermal administration of toxoid may be used successfully as an initial means of promoting immunity or as an ancillary method of immunization.

DISCUSSION

DR. CHARLES CORY, Saginaw, Mich.: During a recent epidemic of diphtheria I saw a number of children with negative reactions to the Schick test in whom the disease developed. I should like to ask Dr. Cowie how much one can depend on the negative Schick reaction.

DR. D. MURRAY COWIE, Ann Arbor, Mich.: I think all pediatricians have seen children with negative Schick reactions who contracted diphtheria, children whose reactions were negative without toxoid immunization as well as children

whose reactions became negative after immunization. When one reviews a large series of cases in which the history is adequate this situation is always encountered, but the incidence of diphtheria among well immunized children is much smaller than among those who are not immunized. In immunization against diphtheria there is a quantitative factor, for some children with negative Schick reactions have less antitoxin than others. My advice would be to continue with immunization but to make careful observations, to check up on them well and to make another report on this subject at the next meeting of this society. There may be some such thing as a community reaction to diphtheria immunization.

DR. STANLEY D. GIFFEN, Toledo, Ohio: For the past few years I have been immunizing against scarlet fever by injecting intradermally 0.1 cc. from each of the five bottles of scarlet fever Streptococcus toxin (containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000 to 120,000 skin test doses per cubic centimeter). I have seen no constitutional reactions, and the local reactions have been moderate. One fussy family discontinued the immunization after the third injection because of a "very sore arm." The immunity produced, as shown by the Dick test, is at least as high as when 1 cc. of toxin is injected hypodermically.

A Case of Hypoglycemia: Follow-Up Report. DR. ROBERT S. SIMPSON, Battle Creek, Mich.

At the 1938 meeting of this society I presented the case of a 15 month old girl with hypoglycemia. She had convulsions from the age of 6 months, and her average fasting blood sugar over a period of nine months was 31 mg. per hundred cubic centimeters. Various measures, including the feeding of a low sugar–high fat diet and a high protein diet, frequent feedings and administration of sedatives and epinephrine, were used. The best results were obtained by feeding an average diet and using epinephrine when she appeared irritable or stuporous.

On June 17, 1938 the patient was operated on, and the tail, body and half the neck of the pancreas were removed. No unusual hypertrophy and no adenomas were found in the tissue removed. After operation no convulsions occurred, although the fasting levels of blood sugar, determined at intervals of a few weeks, varied from 24 to 47 mg. per hundred cubic centimeters.

In March 1939 the child had a mild attack of bronchitis for four days and then suddenly had a series of generalized convulsions, which recurred intermittently for six hours. The convulsions could be stopped by the intravenous administration of a 50 per cent solution of dextrose, but they would start again in five or ten minutes. After the administration of 120 cc. of a 50 per cent solution of dextrose the convulsions ceased. The child was up and playing the following morning, and her blood sugar was 51 mg. per hundred cubic centimeters. During the two weeks in the hospital the blood sugar varied from 34 to 51 mg. per hundred cubic centimeters. During the next seven months she gained normally, and the blood sugar averaged 41 mg. per hundred cubic centimeters.

On Oct. 13, 1939 the child was admitted to the hospital with influenzal bronchitis; she was having constant convulsions. She was cyanotic, and the heart action was irregular and weak. The blood sugar on admission was 100 mg. per hundred cubic centimeters. The convulsions were uncontrolled by the administration of a hypertonic solution of dextrose and sedatives. She died four hours after entry to the hospital.

The results of examinations after death, reported by Dr. A. Humphrey, may be summarized as follows: There was a slight increase of fluid in the thoracic cavity. The heart was normal on both gross and microscopic examination. The abdomen contained a small amount of clear fluid; the peritoneum, liver and spleen were normal, and there was no fat replacement or increase in connective tissue in the liver. The gastrointestinal tract was normal, showing no evidence of diverticula or aberrant pancreatic tissue. There were scarcely any adhesions about the pancreas, which appeared almost normal in size, weighed 17 Gm. and measured 7 cm. in length. The pancreas showed no hyperplasia or hypertrophy of the islet tissue

on microscopic examination. The kidneys were normal, and the adrenal glands appeared slightly enlarged. Examination of the head was not permitted.

Clinically, the child was improved by operation, and I am convinced that a more complete removal of the pancreas would have been life saving. There was a definite hypertrophy of the pancreas in the period between operation and death.

The role of the pituitary in this disease I do not understand, and I regret that it was not possible to examine this gland at autopsy. At the suggestion of Dr. Watson, my associates and I were planning to try the use of pituitary substance at the time of the child's death.

DR. ERNEST H. WATSON, Detroit: I am much interested in Dr. Simpson's final report on this case. The work of Young in England has suggested the possibility of endocrine therapy in such cases. Young was able by employing a freshly prepared extract of the pituitary gland to produce temporary or permanent diabetes mellitus in dogs. It was necessary to use large doses of the extract and to increase them stepwise at short intervals. As I recall, in these dogs with diabetes there were fibrotic changes in the islet tissue. It is known that under certain conditions the pituitary exerts an unfavorable influence on carbohydrate metabolism. Some investigators have expressed the belief that there is a diabetogenic hormone produced in the pituitary gland. I believe that careful study of the effects of administering pituitary extract in cases of hyperinsulinism might be worth while.

DR. C. W. CORY, Saginaw, Mich.: Was a high fat–low carbohydrate diet tried with this patient, with the object in mind of maintaining a low blood sugar level and eliminating the initial stimulation of the pancreas occasioned by the high carbohydrate diet and thus attempting to decrease the magnitude of the drop in the blood sugar and alleviating the convulsions?

DR. ROBERT S. SIMPSON: In regard to Dr. Cory's question about the high fat–low carbohydrate diet, Dr. Mellencamp and I tried this at the University Hospital, without success. Generally, this diet and treatment with insulin do not work well in the cases of severe hypoglycemia.

CHICAGO PEDIATRIC SOCIETY

PHILIP ROSENBLUM, *President*

BENGT HAMILTON, *Secretary*

Regular Meeting, Jan. 21, 1941

Chemotherapy of Pneumonia in Infants Under One Year of Age. DR. W. B. RAYCRAFT (inaugural thesis), DR. W. MOTEL and Dr. JOSEPH GREENGARD.

In the infants with pneumonia in the Cook County Children's Hospital the mortality has always been high. For 1937 and 1938, prior to the use of chemotherapy, the mortality rates were 32 and 31 per cent, respectively. The infants, all under 1 year of age, were drawn from essentially the same group and were managed by the same medical personnel and according to the same therapeutic procedures, other than the use of specific chemotherapy, as those of the 1940 series which is the subject of this paper. While it is true that the incidence of and mortality from pneumonia vary somewhat from season to season, these figures serve in part as a base line from which some conclusions may be drawn in regard to a human experiment in which adequate control is practically impossible.

With the advent of specific therapy, particularly specific chemotherapy, there was a distinct change in the outlook for the babies with pneumonia. Serum therapy never was of outstanding value for patients of this age group because of the difficulty in obtaining material for typing the organisms. Administration of

sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine), however, can be initiated quickly without the necessity of knowing exactly what organism is present in a given case.

This report consists of an analysis of the results obtained with a series of 289 infants observed from March 1939 to July 1940 for whom sulfapyridine was used; the following conclusions were reached:

1. In a series of 200 infants treated in 1940 with sulfapyridine there was a mortality of 10 per cent; when deaths occurring during the first twenty-four hours in the hospital were excluded, the mortality was 7.5 per cent.

2. Of a series of 89 patients, of whom 46 received sulfapyridine and 43 served as controls, those receiving the drug had a definitely shorter febrile period and stay in the hospital.

3. Of the 20 infants who died, 3 showed no response to considerable amounts of the drug. The disease of 2 was of pneumococcic origin, and from the sputum of 1 a staphylococcus was recovered. Seven of the 20 received no sulfapyridine.

4. Toxic effects from sulfapyridine are rare in infants.

Pneumonia in Older Infants and Children in Cook County Children's Hospital. Dr. Craig D. Butler (inaugural thesis).

In a fourteen month period 731 children more than 1 year of age who had pneumonia were treated in Cook County Children's Hospital; the disease of 45 per cent of this number was classified as bronchopneumonia and of 55 per cent as lobar pneumonia. Specimens of mucus from the pharynx were obtained on admission and were examined by the laboratories of the Illinois Department of Health.

Pneumococci were demonstrated in 78 per cent of the specimens, single strains being found in 63 per cent and two or more types in 15 per cent. Other bacteria, chiefly streptococci and staphylococci, were found in 17 per cent, while no bacteriologic diagnosis was made for 5 per cent. Types I, VI, XIV and XIX were found in 45 per cent of the single strain infections and ranked in frequency in the order named. This differs from the reported frequency of types among adults in the same hospital, for whom Dr. Volini has reported types I, II, III and VII as being the most common.

Type I pneumonia affected older children chiefly, 75 per cent of the patients being more than 4 years of age. Lobar pneumonia was present in 80 per cent. The patients appeared more seriously ill than most of those with pneumonia of the other types; the highest incidence of meningismus, coma, delirium, vomiting and abdominal pain was in this group; in 29 per cent empyema developed. Types VI and XIV pneumonias were most common among the patients less than 4 years of age, and the incidence of bronchial and of lobar involvement among patients with these types was about the same. Type XIV pneumonia is distinctly a disease of the young child; in 85 per cent of the cases the patient was under 4 years of age, yet in 69 per cent the diagnosis was lobar pneumonia. Bronchopneumonia predominated among patients whose disease was caused by pneumococci of the higher number types.

Cultures of blood drawn on admission were positive in only 32 cases, in 22 of which the organism was a pneumococcus. In 8 cases in which there was a positive blood culture empyema developed, but in 17 no clinical evidence of sepsis was shown and the patient left the hospital within eight days.

Acetone was present in the urine in 60 per cent and albumin in 6 per cent of the cases on admission. Blood counts on admission showed that in 25 per cent there were less than 10,000 leukocytes per cubic millimeter.

Suppurative otitis media was a complication in 7.4 per cent of the cases. Its frequency varied inversely with the age of the patient, and it was most common in the cases of infection of the types frequent among the younger group, especially types XIV and XIX, but bore no other striking relation to the bacteriologic data.

Empyema was a complication in 29 cases, or 4 per cent, of which 62 per cent were of type I pneumonia. In 10 cases an organism was recovered from the empyema fluid which had not been demonstrated in the sputum. In 4 cases of empyema the patient died; in the others recovery ensued after surgical intervention.

Sulfapyridine in customary dosage was administered in 656 of the 731 cases. In 19 antipneumococcus rabbit serum was also given. In 75 no specific treatment was used. Symptomatic and supportive therapy was used when indicated. Vomiting was a troublesome, but not serious, effect of the drug. Delirium, coma, hematuria and cutaneous eruptions occurred in a few cases but did not greatly interfere with treatment.

Serum was given in those cases in which a favorable response to chemotherapy was not shown within twenty-four to forty-eight hours.

In about one third of the cases in which chemotherapy was used the patient became afebrile in twelve hours, in two thirds within twenty-four hours and in more than 90 per cent within forty-eight hours. Twenty patients died, a mortality of 2.73 per cent. Of these, 9 died within twenty-four hours of admission and 2 died of doubtfully related complications after readmission to the hospital. Nine patients died during active treatment, a net mortality of 1.33 per cent. Of the patients 4 years of age or older, only 1 died, a patient with streptococcic sepsis with empyema.

Recent Trends in the Treatment of Pneumonia. Dr. Samuel J. Hoffman.

Until recently the therapy of pneumonia was entirely empiric. The value of serotherapy in pneumonia of the more severe types has definitely been established. There have been many unfavorable experiences with horse serum. Rabbit serum is therefore preferred because of its lesser toxicity, its greater efficacy and the fewer allergic complications following its use.

Various organisms may cause the infections. Type I and type XIV pneumococci are most commonly found in cases of pneumonia in children. Serum is particularly recommended for young infants, among whom the mortality is high, and for patients with positive blood cultures. The advantages and disadvantages of serum are pointed out and treatment with sulfapyridine discussed in detail. Culture of the sputum and typing of the organism should be done at the outset. The use of serum and chemotherapy should be combined when indicated.

Sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole) therapy is also discussed and the dosage for oral and for intravenous administration taken up in detail.

In the last analysis, the case of each patient should be considered as an individual problem and everyday common sense exercised. Other important aids in the therapy of pneumonia, such as oxygen, transfusions and administration of dextrose, should not be overlooked even though chemotherapy is being used.

Technical Aspects of Pneumonia Management. Dr. Sol P. Ditkowsky (by invitation).

The importance of determining the agent responsible in a case of pneumonia is stressed in view of the present day knowledge of chemotherapy and serotherapy. Blood for culture should be drawn before the initiation of treatment because by culture the type of organism may be determined in some instances and information of value for prognosis may be obtained.

The relative values of material for culture obtained by the laryngoscopic method or the gag method with a tongue depressor and that secured by the nasopharyngeal technic are considered. The results show the superiority of using material from the larynx, whether obtained with the laryngoscope or by the gag method, over that of using material from the nasopharynx. The technic of lung puncture is discussed and evaluated; it is believed that this method should be used only when the indications are clearcut.

The fact is stressed that the use of sulfapyridine did not interfere with the typing of pneumococci. If a patient did not respond to drug therapy, the failure was evaluated on the basis of the adequacy of drug treatment, the presence of complications and the possible impairment of the immunologic response.

The adequacy of treatment was evaluated by determination of the concentration of the drug in the blood, while evaluation of the immunologic response was aided by such measures as the Francis and the agglutination test. The technics of these tests are described; it is believed that the Francis test, while not infallible, gives important evidence about the immunologic response and the adequacy of serum treatment and should be used more frequently.

The indications, contraindications and value of serum therapy are discussed.

It should be noted that such general measures as control of dehydration, correction of disturbances of acid-base balance and blood transfusion are important in reducing mortality. Attention should also be called to the almost specific action of blood transfusion in cases of type XIV pneumonia in children.

DISCUSSION OF PAPERS BY DRS. RAYCRAFT, MOTEL AND GREENGARD; BUTLER; HOFFMAN, AND DITKOWSKY

DR. NOEL SHAW: First, I should like to compliment the speakers on these splendid papers, which cover the problems of the treatment of pneumonia both in infants and in older children at Cook County Children's Hospital. This group of approximately 1,000 cases is one of the largest single series ever reported on and is certainly one of the largest in which typing of the organism was done and treatment with sulfapyridine was used. There is definite value in a careful clinical and laboratory study of such a large series.

Second, I think these reports are further evidence of the progress made in the Cook County Children's Hospital under the guidance of its chief of staff, Dr. Blatt. In April 1939, the pneumonia service of Drs. Butler and Hoffman was initiated by Dr. Blatt, and it has been my good fortune to examine many of their patients with pneumonia who were over 1 year of age.

Many of the early reports on the treatment of pneumonia in children with sulfapyridine, such as those by Barnett and Hartman, Smith and Nemir and Carey, established the efficacy of such treatment, its relative safety and the dosage to be used. Yet much of this work at Cook County Children's Hospital was pioneer research in the treatment of pneumonia with sulfapyridine and now serves the purpose of confirming the satisfactory results reported by others. In addition, the clinical and laboratory data for so many cases are of great value.

In Dr. Butler's series the staphylococcus was found in 7 of the 32 cases in which there was a positive blood culture. One must not overlook the role of this organism in the production of primary pneumonia or of bronchopneumonia, as Kanof and his associates pointed out (*J. Pediat.* **14**:712 [June] 1939). In the round table discussion on pneumonia led by Carey and Hodes at the 1940 meeting of the American Academy of Pediatrics, in Memphis, Tenn., the role of the staphylococcus in cases of pneumonia was emphasized and the suggestion made that sulfathiazole was probably to be preferred over the other derivatives of sulfanilamide for use in such cases.

In 17 of the 32 cases of bacteremia mentioned by Dr. Butler, there was no clinical evidence of bacteremia, and the patients in these cases left the hospital in eight days. Dowling and his associates (*J. A. M. A.* **115**:2125 [Dec. 21] 1940) found that the use of sulfapyridine alone was as effective as its use in combination with serum in cases of bacteremia. Although it has been repeatedly recommended that serum be given in addition to sulfapyridine when bacteremia is present, their observations on adults tend to cast doubt on the necessity for this unless other factors are present which make for a poor prognosis.

Another important point in Dr. Butler's paper is the fact that of 29 cases of empyema, in 18, or 62 per cent, the pneumonia was of type I. Therefore most physicians feel that if a patient with type I pneumonia has not responded satisfactorily to chemotherapy within eighteen to forty-eight hours, especially if there

is evidence of possible effusion, specific serum should be given without further delay. The importance of routine typing on admission is self evident. However, if empyema has already developed, the use of chemotherapy alone or in combination with serum usually is not sufficient. Aspiration or drainage is still necessary, as has been pointed out by Carey (*J. A. M. A.* **115**:924 [Sept. 14] 1940) and others.

Serum therapy at Cook County Hospital has been supplanted by chemotherapy except in cases in which the response to the latter is unsatisfactory. The lessened cost to the taxpayer of using relatively small total doses of sulfapyridine instead of serum should be appreciated, even in these days of profligate spending.

I should like to make one other point: It is my definite impression that in the majority of cases in which prompt results are obtained with sulfapyridine shortly after the fall in temperature the physical signs and symptoms become less and less pronounced, instead of running the course which is usual in cases of untreated pneumonia. It has been a common observation that on the second day after the drop in temperature practically no rales can be detected in the affected area—only some diminished breath sounds and moderate dulness.

As a tribute to Dr. Ditkowsky, who took personal charge of obtaining material from the throat for typing, it might be stated that in practically 80 per cent of the cases in which he took material for cultures the result was positive, whereas for a time after he left the institution the results of only about 20 per cent of the cultures done by others were positive.

DR. HENRY E. IRISH: I should like to say a word in discussion, since I had the honor of being the presiding genius while some of these low mortality records for infants under 1 year of age were being established. For many years I was in charge of a service for infants at Cook County Children's Hospital, and I am enormously pleased with the lowered mortality figures. In the single month of January 1917 there was a mortality of 72 per cent among the infants admitted. That sounds rather startling, but those who remember the type of disease prevalent then, pneumonia complicated with a Streptococcus haemolyticus infection, will also remember that in many cases the disease was fulminant and the patient lived scarcely long enough to get the bath which was given on admission.

I believe that various factors have been responsible for the difference in mortality since 1918. The decrease between 1918 and 1926 was associated with the decreased incidence of the complication prevalent in that decade, infection with Str. haemolyticus. The decrease between 1926 and 1932 occurred, I think, as a result of adequate oral hydration of the patients. The next step was the introduction of the intravenous administration of fluids and of whole blood, which seemed to be of particular benefit if it was supplied by a donor who had had the same infection within the preceding few weeks.

These measures all seem archaic now, but many physicians remember the linseed poultices which were assiduously applied. Quinine had a place, and aconite and veratrum viride, and then came alkalis and salicylates and digitalization of the patient. I heard digitalis mentioned tonight, and I shall only say, on the basis of all my observations, that it never produces digitalization in the sense of inhibition of the vagus in a young infant; it cannot slow the heart.

I greatly enjoyed these papers. It is most creditable to the Chicago Pediatric Society that such a large and well worked-up series of cases should be presented by some of its members who are on the staff of Cook County Children's Hospital.

DR. MAURICE L. BLATT: The essayists are to be congratulated on the results of their treatment of pneumonia and on the clear presentation of their subjects. However, there are a number of other factors which they did not mention which have influenced the mortality rate. These should not be forgotten in the justifiable enthusiasm over the new drug therapy.

It should be remembered that the children with pneumonia entering Cook County Children's Hospital today are in much better physical condition than those who were admitted twenty years ago. Rickets is materially less prevalent, and scurvy has almost disappeared. Subclinical manifestations of rickets are becoming less pronounced as the years go by. Complicating nutritional disorders resulting

from improper feeding preceding the onset of the pneumonia are less common as a result of better public and private infant welfare, advanced knowledge in infant feeding and a better milk supply. Children enter the hospital earlier in the course of the disease than they did a number of years ago. The prejudice against hospitalization, so prevalent even ten years ago, has almost disappeared, and families now request that their children be sent to the hospital. The number of hours of nursing care has increased. The use of the intravenous and subcutaneous administration of fluids and medicaments has been increased and the technic has been improved. The more common use of oxygen for seriously ill patients has also been a factor in reducing mortality.

DR. E. T. MCENERY: I should like to make one comment on Dr. Irish's discussion. He forgot to mention the large doses of camphor in oil which were used. These papers contain a tremendous amount of information which I am sure will be of benefit to those who heard them. As to the question of complications, especially empyema, in Children's Memorial Hospital there were about 45 to 50 cases of empyema a year. Last year the incidence dropped to 18. The statement made by Dr. Ditkowsky that once empyema starts it is hard to clear it up by administering sulfapyridine is true, but there are many cases in which aspiration will yield fluid which is not purulent. Another point is that the type of organism in the aspirated fluid is sometimes entirely different from that in the sputum.

DR. PHILIP ROSENBLUM: I should like to ask Dr. Hoyne about his experience with sulfapyridine in cases in which pneumonia followed a contagious disease.

DR. ARCHIBALD L. HOYNE: It seems to me that the presence of a contagious disease does not alter the treatment of pneumonia a great deal. The points brought out in the papers just read apply to patients with contagious diseases as well as to others. It is true, however, that considerable confusion existed sometimes in the past when one encountered as a complication in a patient with a contagious disease a condition which might readily occur independently. Years ago it was difficult to secure surgical intervention for a patient with a contagious disease who might, for example, require appendectomy. In the cases in which pneumonia is the complication I think the chief question would be simply the choice between sulfapyridine, sulfathiazole and sulfanilamide. The decision might be influenced by the character of the contagious disease present.

Book Reviews

Clinical Pellagra. By Dr. Seale Harris, assisted by Dr. Seale Harris Jr., with a foreword by Dr. E. V. McCollum. Price, $7. Pp. 494, with 66 illustrations, 4 color plates and 17 tables. St. Louis: C. V. Mosby Company, 1941.

The primary purpose of the monograph is to assemble the data relative to pellagra which have accumulated since the well known work of H. F. Harris, "Pellagra," was published in 1919. The book is intended to provide the physician with information which is accurate and dependable. To accomplish his purpose the author has taken full advantage of his wide clinical experience, gained during the many years which he has devoted to the study of pellagra. The opinions expressed are in most instances in accord with those held by clinicians at present. The author believes that the final word about the cause of pellagra has not yet been written and that the lack of certain intrinsic factors found in the stomach and liver is as important as a deficiency of nicotinic acid in production of pellagra.

Nine collaborators shared in the preparation of the monograph. All of them have played monumental roles in the study of pellagra in the United States.

The subject matter is arranged in seven sections, with a foreword by E. V. McCollum and an introduction by the author. A rather large part of the book deals with the theories about the nature of pellagra and a detailed account of the investigative work which supports them.

The author's views on the genesis of pellagra are revealed in a chapter devoted to this subject. In the chapters dealing with the symptoms, complications, diagnosis, prophylaxis and treatment of pellagra, one finds clinical information of the most practical sort. Stress is placed on the importance of an adequately regulated diet as a prophylactic and a therapeutic measure.

The pediatrician will enjoy the chapter on pellagra in children, which was written by one of the well known collaborators.

The literary style of the work is pleasing, at times intimately conversational. The text on the whole is lively and readable, although in certain instances the arrangement of the subject matter could have been improved.

A bibliography of the most important articles on pellagra is appended. The illustrations are for the most part clear and adequately illuminate the text.

The author's enthusiasm and clear understanding of his subject are evident to his reader, and the book should be of value to students and to physicians who treat patients with pellagra.

Proceedings of the Dental Centenary Celebration, Sponsored by the Maryland State Dental Association and the American Dental Association. Edited by George M. Anderson. Price, $5. Pp. 1061, with 505 illustrations. Baltimore: The Waverly Press, 1940.

The volume includes the complete transactions of the Dental Centenary Celebration held under the auspices of the Maryland State Dental Association and the American Dental Association in commemoration of one hundred years of American dentistry. Included, in addition, are the transactions of the meeting of the American College of Dentists held at the same time. The presentations offered in the scientific sessions include a valuable group of papers contributed by leaders in dental and medical education and practice. They were in general prepared to provide a cross sectional view of contemporary dental science. Outstanding are the papers by Isaac Schour and Maury Massler dealing with the effect of the endocrine glands on the teeth, the jaws and the facial skeleton; by the late Rudolf Kronfeld on the correlation between clinical and pathologic diagnosis of

chronic apical periodontitis, and by Edward C. Rosenow on focal infection and elective localization in relation to systemic disease (a review and results of further studies). Many other excellent papers are included. There is a fine presentation on the history of anesthesia by W. Harry Archer.

The sections dealing with ceramics and the clinical phases of dentistry, including orthodontics, offer many valuable additions to dental literature. Perhaps never before has there been assembled as fine a collection of exhibits; particularly meritorious are those dealing with the historical background of dental science. Photographs of these exhibits have been reproduced, with a brief explanatory note for each. There is included also a historical play which was produced by the Maryland State Dental Society and a historical sketch of the foundations of professional dentistry.

The book as a whole is a fitting memento of what may be considered the most outstanding dental meeting in American history. It differs from the uninteresting reading typical of transactions because of its reflection of the color and the human interest which characterized the meeting. It is deserving of note because of the high quality of the scientific presentations.

La obra de las colonias infantiles en Cuba durante los anos 1934-1939. By Dr. Carlos Hernandez Miyares, President of the Council of Direction and Medical Director of the National Guardianship of Children's Colonies. Price, none given. Pp. 43, with 9 illustrations. Habana, Cuba: Molina y Compania, 1940.

The author of this monograph presented a report on the achievements and activities of the health camps (as they are known in this country) before the section of social and preventive medicine of the First Cuban Congress of Regional Pathology, Social Medicine and Public and Private Hygiene, held in Santiago, Cuba, March 6 to 9, 1940. In this report the workings of the camps are given in great detail, and their activities are listed in numerous tables.

Dr. Miyares has a good grasp of the principles of public health, as is shown by the exclusion of children with active tuberculosis and syphilis from the camps and the administration of diphtheria toxoid to all those admitted who have a positive reaction to the Schick test. He made a plea that all children with intestinal worms seeking admission to the camps (75.54 per cent of the applicants) be allowed to enter. They were admitted and received treatment for the first fifteen days of their stay. The children's teeth were well cared for; of 8,058 children admitted during the past five years 5,602 received dental treatment.

A plea should be made for the establishment of permanent health camps in this country similar to those in Cuba. It is stated that the building up and strengthening of the children during their stay in the camps enable them to store up physical energy and resistance, which aid in the fight against tuberculosis. No mention is made of immunization against typhoid, typus fever or scarlet fever, which often occur in Mexico and South American countries.

Modern Diagnosis. Edited by Sir Humphry Rolleston and Alan Moncrieff. Price 12s. 6d. net. Pp. 268, with 29 illustrations. London: *The Practitioner*, in conjunction with Eyre & Spottiswoode, Ltd., 1940.

This book is the fifth in a series of handbooks published in behalf of *The Practitioner*. The editors have attempted to produce a practical, up-to-date manual devoted to those conditions which are most likely to confuse the student and the general practitioner. Because of the wide scope of the rather small volume the treatment of each item is, of necessity, brief. Migraine, for example, is dismissed in a little more than one and one-half pages. The concise style reflects careful study and a boiling down of the material to its essentials, a welcome virtue.

The book is in two parts. Part 1, which is on clinical diagnosis, consists of short monographs on the diagnostic significance of the knee jerk, diagnosis in diseases of the skin and in facial conditions, the diagnostic importance of the

tongue, changes in the nails as an aid to diagnosis, pains about the head and neck, abdominal pain and cardiac murmurs and swellings and sinuses in the neck in childhood. Part 2, which is concerned with laboratory and special diagnosis, consists of short monographs on laboratory tests, aids and methods in the diagnosis and treatment of tuberculosis, disorders of the gastrointestinal tract, diseases of the liver and gallbladder, chronic rheumatism and the diseases of children; the estimation of renal function; the differential diagnosis of glycosuria; biochemical examinations by the general practitioner in diabetes mellitis, the technic of collecting and examining blood, the value of the electrocardiogram in general practice, and the meaning and interpretation of the basal metabolic rate. All of the twenty short monographs are written by men working in the respective special fields.

"Modern Diagnosis" is an excellent book for students but does not seem comprehensive enough for the practicing physician.

The American College of Physicians: Its First Quarter Century. By Dr. William Gerry Morgan. Price, $2. Pp. 276, with 72 illustrations. Philadelphia: American College of Physicians, 1940.

This volume retails the history of the American College of Physicians during the first quarter century of its existence. In the first chapter Dr. Morgan describes the founding and subsequent events in the development of the organization. One of the most constructive contributions of the college is the part it played in the establishment of the American Board of Internal Medicine.

The organization took as its model the Royal College of Physicians in Great Britain, fellowship in which denotes a high level of accomplishment and membership in which is attained only by those who pass a rigid examination.

The functions of the College are stated to be the conduct of sectional meetings, the conferring of fellowships and the sponsoring of postgraduate courses of instruction in this country and abroad; it also proposes to engage in public health activities when opportunity affords.

The book contains intimate details of the organization, a list of the officers of the College and of its publications and general information which will be of interest to those who are already affiliated with the organization as well as to those who hope to become members.

Bacillary and Rickettsial Infections. By Dr. William H. Holmes. Price, $6. Pp. 676, with no illustrations. New York: The Macmillan Company, 1940.

It is a refreshing experience to read a text for medical students written as well as this one is. There is none of the dry listing of data or fear of literary style so common in most textbooks. Dr. Holmes has not only presented adequately the relevant facts but has managed to place them in their proper historical background. Possibly he has devoted too much space to the history of each disease, but in so doing he has produced a most interesting book, which holds and stimulates the reader's interest in an unusual way. This was the acknowledged purpose of this type of presentation, namely, to stimulate and to interest the medical student by offering a clinical picture of disease as seen in historical perspective. In this Dr. Holmes has been eminently successful.

The material indicated in the title is adequately, but not exhaustively, covered. The discussion of the infections due to Pasteurella, Rickettsia and Brucella is especially well done. Illustrations have been omitted for the sake of brevity. As an unusual and stimulating text for medical students and as a most interesting and readable book for the clinician, this volume can be heartily recommended.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Prof. Dr. J. van Lookeren Campagne, Hofstraat 16, Gröningen, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Av. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Julius H. Hess, 104 S. Michigan Ave., Chicago.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Cleveland. Time: June 2-6, 1941.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Richard M. Smith, 66 Commonwealth Ave., Boston.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Statler Hotel, Boston. Time: Oct. 9-11, 1941.
Region I. Place: Philadelphia.
Region II. Place: John Marshall Hotel, Richmond, Va. Time: April 24-25, 1941.
Region III. Place: Palmer House, Chicago. Time: May 15-17, 1941.
Region IV. Place: Fairmont Hotel, San Francisco. Time: May 1-3, 1941.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Hot Springs, Va. Time: May 22-24, 1941.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.
Place: Brockville, Ontario. Time: June 14, 1941.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. A. Ashley Weech, 3975 Broadway, New York.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Chalfonte-Haddon Hall Hotel, Atlantic City, N. J. Time: May 6-7, 1941.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.
Place: Doernbecker Hospital and University of Oregon Medical School, Portland. Time: Jan. 25, 1941.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.
Place: Del Monte. Time: May 1941.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. D. C. Darrow, 789 Howard Ave., New Haven.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.
Place: Chicago. Time: May 1941.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. H. Aubrey White, Alexandria.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New York.
Place: Shreveport. Time: April 1941.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1941.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.
Place: Biloxi. Time: May 12, 1941.

Nebraska Pediatric Society

President: Dr. J. C. Iwersen, 236 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. C. P. Jasperson, 509 Nixon Bldg., Corpus Christi.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Fort Worth. Time: May 14, 1941.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Greene, 910 Grand Concourse, New York.
Secretary: Dr. F. E. Chick, 2325 University Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Philip Rosenblum, 2376 E. 71st St., Chicago.
Secretary: Dr. A. L. Newcomb, 1791 W. Howard St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

DALLAS PEDIATRIC SOCIETY

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Robert J. Mason, 460 Birmingham Rd., Birmingham, Mich.
Secretary: Dr. J. Hugh Lewis, 2966 Biddle Ave., Wyandotte, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

FULTON COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (ATLANTA, GA.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. R. P. Schowalter, 411 E. Mason St., Milwaukee.
Secretary-Treasurer: Dr. George H. Wegmann, 2650 W. Hopkins St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harold Flanagan, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Secretary-Treasurer: Dr. George B. Logan, Mayo Clinic, Rochester, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barba, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.